Interrelationships and Effects of Accelerated Rehabilitation Conditioning and Gene Polymorphism on Functional and Physical Responsiveness of People Recovering from Anterior Cruciate Ligament Reconstruction Surgery

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Abstract of the thesis

Chapter one of this thesis offered a general insight on the anterior cruciate ligament (ACL) injury and the outcome measures of ACL rehabilitation while chapter two was a systematic review on the effects of “accelerated rehabilitation” after ACL reconstruction surgery. The review concluded that 5 out of 10 randomised control trial studies had demonstrated moderate relative effect sizes in terms of improved knee laxity, neuromuscular performance, range of motion and some patient-reported outcome measures following accelerated rehabilitation for patients with ACL reconstruction. Chapter three was a systematic review in which the genetic influence on responsiveness to strength conditioning and the outcomes of knee after ACL reconstruction were investigated. The findings revealed that intra-genotypic responses to strength conditioning were heterogeneous and that duration, intensity and frequency of strength conditioning were factors that contributed to the differential responses of genotypes in regulating gains in strength.

Chapter four (study one) was a randomised control trial in which the effects of quantified accelerated conditioning rehabilitation, anthropometric and orthopaedic-related factors on the outcomes of knee performance were investigated following ACL reconstruction. Participants (n= 40) were prescribed either accelerated rehabilitation in the first 12 weeks post-surgery (n=20) or contemporary (n=20) ACL rehabilitation. Participants were assessed in four different testing occasions; pre-surgery (0), 6, 12 and 24 weeks post-surgery. The findings revealed there was significant group by leg by time interaction using ANOVA and repeated measures on the latter two factors with superior scores in the accelerated group for the change scores of some sub-sections of KOOS. When controlling for body mass, waiting time and unstructured physical activity, scores associated with objective neuromuscular measures showed significant interaction (group by time by leg) from pre-surgery to 12 weeks post-surgery with superior scores favouring the accelerated group. This showed that the accelerated rehabilitation offered advantages over the contemporary practice coincident with enhanced conditioning and that orthopaedic-related factors were influential in determining the outcomes of ACL rehabilitation.

Chapter five (study two) explored the correlation amongst the objective and subjective functional and objective neuromuscular outcome measures. Participants from study one (n=40) took part in this study. While there was no correlation between the change scores of the objective functional (single leg hop) and the subjective functional (KOOS, K-SES, Lyhsholm, IKDC) outcome measures, the absolute scores associated with sub-sections of KOOS had shown the most consistent correlation with objective measures (KOOS and sensorimotor performance [SMP] of the quadriceps;-0.46, peak force of the quadriceps; -0.34, and anterior tibio-femoral displacement [ATFD]; -0.32). Change scores for SMP and KOOS and for the single leg hop and Lysholm showed the highest correlation in the hierarchy of objectively-measured determinants of knee functional performance. Overall, there was a lack of robust and significant linkage amongst the functional and objective neuromuscular outcome measures.

Chapter six (study three) investigated the influence of angiotensin converting enzyme (ACE) I/D gene polymorphisms on the responsiveness of function and physical performance to rehabilitation training following ACL reconstruction. Participants (n=40) from the previous two studies participated in this study that involved obtaining blood samples for DNA and genotyping for ACE I/D polymorphism. The findings revealed that one (peak force for quadriceps) out of 5 objective functional and neuromuscular measures had shown significant interaction (ACE genotype by time by leg) in response to rehabilitative training favouring the D allele over the I allele group. It was concluded from this exploratory trial that there was some evidence to suggest that planning for ACLR rehabilitative care might be optimised by using the conditioning-response characteristics associated with the individual's genotype of the ACE I/D. There was a 15% of variance in the peak force (quadriceps at 12 to 24 weeks post-surgery) favouring the D allele group, indicating that strength training could be possibly prescribed routinely earlier to patients carrying the D allele. The last chapter of the thesis (chapter seven) was a general discussion that synthesised the findings of all the three studies of the thesis including their limitations and future directions.

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I would like to offer my especial thanks to my family (Dad, mom, brothers and sisters) for their continuous support and motivation. Finally, I would like to offer my especial thanks to my lovely wife, Aida and two children, Maitha and Yaser. Without their sacrifices and support this would not have been possible. I love you all.

Dedication

I dedicate this work to my beloved parents (Abdullah Salim Al Kitani and Jokha Al Shuwehdi).

I have been blessed and lucky to be one of your children.

The sacrifices, support and care you provided me can never be paid back.

However, I will live to make you both proud of me.

Author’s declaration

PhD THESIS TITLE: INTERRELATIONSHIPS AND EFFECTS OF ACCELERATED REHABILITATION CONDITIONING AND GENE POLYMORPHISM ON FUNCTIONAL AND PHYSICAL RESPONSIVENESS OF PEOPLE RECOVERING FROM ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION SURGERY.

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Abbreviations

ACC	Accident Compensatory Corporation
ACL	Anterior Cruciate Ligament
ADL	Activities of Daily Living
AMB	Antero-medial Bundle
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATFD	Anterior Tibio-Femoral Displacement
BMI	Body Mass Index
BPBT	Bone-Patella Bone-Tendon
CONSORT	Consolidated Standards of Reporting Trials
EMD	Electromechanical Delay
EMG	Electromyography
FIT	Frequency, Intensity, Time
ICC	Intra-class Correlation Coefficient
IKDC	International Knee Documentation Committee
KOOS	Knee injury and Osteoarthritis Outcome Score
K-SES	Knee Self-Efficacy Scale
MCID	Minimally Clinically Important Difference
MDC	Minimal Detectable Change

MHLC	Multidimensional Health Locus of Control
MVMA	Maximal Voluntary Muscle Activation
NHS	National Health Service
NNKLR	Norwegian National Knee Ligament Registry
PEDro	Physiotherapy Evidence Database rating scale
PF	Peak force
PLB	Postero-lateral Bundle
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RFD	Rate of Force Development
RJAH	Robert Jones and Agnes Hunt
SD	Standard Deviation
SEM	Standard Error of Measurement
VAS	Visual Analogue Scale

1 Chapter One: General Introduction

1.1 Anatomy and the function of ACL

The knee joint is a very complex joint which incorporates a wide range of ligaments that help to stabilise and control the joint's movements. The four main ligaments of the knee that connect the femur to the tibia include the medial collateral ligament which runs on the inner parts of the knee, the lateral collateral ligament which runs on the outer parts of the knee, the posterior cruciate ligament (PCL) and the anterior cruciate ligament (ACL) which both run along the middle of the knee joint [intra-articular ligaments]. Figure 1.1 illustrates the anterior view of the right knee. ACL is a band-like structure that runs from the inner posterior part of the lateral condyle of the femur to the inter-spinous area of the tibia (Siegel et al. 2012). The main function of ACL is to prevent an excessive anterior translation of the tibia in relation to the femur and to limit excessive external tibial rotation of the knee joint during motion. This is achieved by the work of its two functionally distinct bundles; 1) the antero-medial bundle (AMB) and 2) the postero-lateral bundle (PLB). AMB which appears tight in flexion is primarily involved in limiting the anterior tibial translation while PLB's main function is to limit and control the tibial rotation in the knee joint (Mathur and Splain 2003).

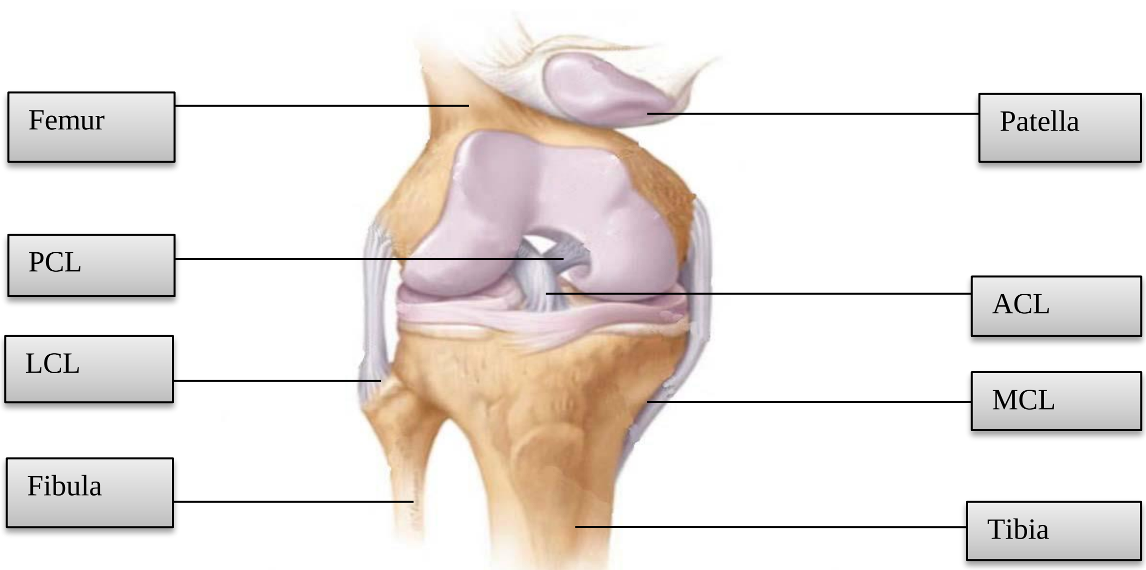


Figure 1.1 Anterior view of the right knee. The patella and patella tendon in this schematic diagram are lifted to expose the intra-articular structures of the knee joint. Image (Adapted from Calmbach and Hutchens (2003).

1.2 Incidence and mechanism of ACL injury

It is estimated that about 80,000 people sustain an ACL injury per year in the United States (Shimokochi et al. 2008). However, it is extremely difficult to determine the incidence of ACL injuries in any country if comprehensive injury registries are not in place. New Zealand is one of the countries that provide accurate epidemiological data of their nation through a registry system called the accident compensatory commission (ACC). Recently a study to determine the national epidemiology of knee ligament injuries in New Zealand was carried out by Gianotti et al. (2009). Data from ACC revealed that 37 people in 100,000 sustain an ACL knee injury per year with the majority (65%) occurring while people are involved in either recreational or sporting activities. Similarly Norway has advocated a national registry of knee ligament injuries and reported an incidence of 34 ACL ruptures in 100,000 citizens (Granan et al. 2008). It is worth noting that the national registries of ACL incidence data in both countries have shown a remarkably similar injury rate. With regards to gender specific incidence of ACL injuries, it is widely accepted that males are more prone to ACL injury in the general population than their counterparts, possibly due to their greater sports participation and the involvement of males in high risk activities including cutting, landing and pivoting movements. Interestingly however, females have been shown to have a higher incidence rate of ACL injury than males when comparing both genders' participation in the same sporting event (de Loes et al. 2000).

With respect to the biomechanics of ACL rupture, the injury typically occurs because of an abrupt deceleration, alteration of direction and/or awkward landing from a jump (Silva et al. 2012, Alentorn-Geli et al. 2009a, Silvers and Mandelbaum 2007). With the majority of ACL injuries occurring in the pattern of a non-contact mechanism [accounting for 80% of all ACL injuries (Alentorn-Geli et al. 2009b)], it is generally accepted that non-contact ACL injuries occur in a position in which the knee is extended during the movement of landing from a jump, pivoting or the abrupt change of direction or deceleration, where the knee muscle stiffness and there is high quadriceps muscle activity relative to hamstring muscle activity (Silvers and Mandelbaum 2007). In a review study by Alentorn-Geli et al. (2009a) which was based on several approaches including interviews with injured athletes, video analysis and clinical studies, the study concluded that there are four main movements that contribute and lead to ACL injuries. These are 1) dynamic valgus knee, 2) external rotation of foot relative to the knee, 3) slight flexion of the knee joint (less than 30 degrees) and 4) landing or deceleration while centre of gravity is behind the knee joint. Because neuromuscular control and performance is one of the main performance indices of the trials of this thesis, this index will be discussed in further details in the upcoming chapters.

1.3 Risk factors for ACL injury

It is widely accepted that the exact mechanisms and aetiology that lead to ACL injuries are still unknown. The majority of research studies have been conducted in order to establish potential risk factors that will allow for a better understanding of the mechanisms for ACL injuries. Various risk factors for ACL injuries have been widely reported within the literature. Based on the guidelines given at Hunt Valley meeting (Griffin et al. 2006), this chapter has classified risk factors into the followings: environmental, hormonal, neuromuscular, anatomical and biomechanical. However because of the limited scope of this literature review, the focus will only be on factors that are deemed relevant to the thesis. This will include discussing the environmental, anatomical, neuromuscular and genetic factors. In addition, genetic risk factors will be included in this thesis for reasons that will be explained later. Anatomical factors include the quadriceps Q angle, notch width, ACL size, tibial slope, foot pronation and generalised joint laxity (Silvers and Mandelbaum 2007, Siegel et al. 2012). With regards to the extrinsic factors, environmental risk factors including weather conditions, footwear and playing surfaces have been reported in the literature (Alentorn-Geli et al. 2009a, Silvers and Mandelbaum 2007). Neuromuscular control can be defined as the unconscious state of activating the dynamic restraints surrounding a joint in response to sensory stimuli (Alentorn-Geli et al. 2009a), hence this control plays an important role in the biomechanics of physical activity movements. Differences in neuromuscular control, exhibited by the unconscious muscle activation, can help explain the increased risk of ACL injury (Griffin et al. 2006). Neuromuscular control is partially a modifiable factor, meaning that it is possible to some extent, through specialised proprioceptive exercises, an improvement might occur in the neuromuscular control of the body (Griffin et al. 2006). The influence of neuromuscular control as an important outcome of successful ACLR rehabilitation will be highlighted in subsequent chapters.

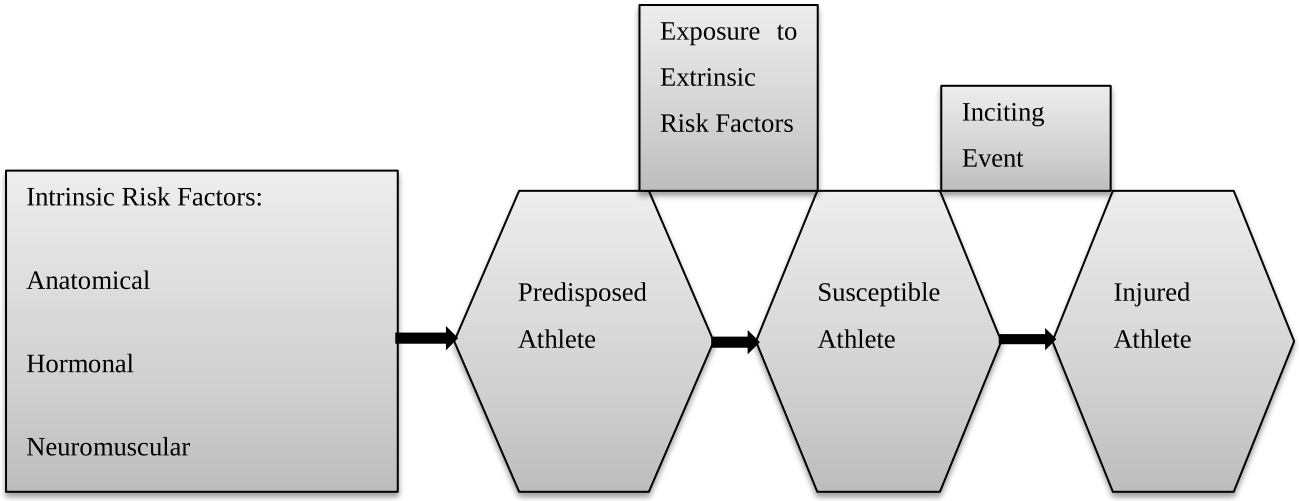


Figure 1.2 The complex relationship between intrinsic risk factors, extrinsic risk factors and a specific inciting event in the causation of ACL ruptures is illustrated in this schematic diagram. The diagram demonstrates that there is a relationship between these factors. The relationship can be explained in that intrinsic and extrinsic risk factors do not separately cause an injury but an inciting event has to take places which subsequently place the ACL under strain. Adapted from the original model proposed by Bahr (2005).

1.4 Genetic component as a risk factor for ACL injury

Recently there has been a focus on identifying the role of genetic element as an intrinsic factor that may have a contributing role in ACL injury (Posthumus et al. 2009, September et al. 2007). For instance, in a study by Khoschnau et al. (2008), the TT genotype of COL1A1 Sp1 binding site polymorphism was found to be under-represented in a group who sustained ACL ligament injuries compared with a group who did not sustain ACL injuries. Of 233 subjects, there was only one participant with an ACL rupture who represented TT genotype of COL1A1 Sp1 binding site polymorphism compared to 6 out of 358 participants in the control group. It is worth mentioning however that the study conducted by Khoschnau et al. (2008) should be treated with caution as there was low frequency of the rare TT genotype amongst the studied population. As such there is low certainty that the COL1A1 Sp1 binding site polymorphism could be classified as a risk factor for ACL ruptures.

In another study, Posthumus et al. (2009) found that TT genotype of COL1A1 Sp1 binding site polymorphism was under-represented in ACL ligament injury groups compared with non-ACL injury group. However the study concluded that it is highly unlikely that a single genetic variation is responsible for association with an altered risk for ACL ruptures. This is because ACL injury are, like most musculoskeletal sports related injuries, regarded as multifactorial disorders. In an attempt to understand the multifactorial nature of the latter injuries, a model was developed by Bahr (2005) to determine all the intrinsic and extrinsic factors that contribute to the causation of the injury (Figure 1.2).

Although it is important to highlight the contributing factor of genetic components when exploring the intrinsic risk factors for ACL injuries, this thesis, however, will focus on the contribution of genetic influences in terms of the rate of responsiveness to strength training within the rehabilitation programme following ACLR surgery.

1.5 Consequences of ACL injury

When a person damages his/her ACL, the injury is most likely associated with an injury to other knee structures including the articular cartilages and or other ligaments surrounding the knee joint. Injury to ACL is often linked to serious consequences including loss of the full range motion, pain and swelling, increased risk of subsequent knee injuries, loss of dynamic stability and the likelihood of developing early onset of knee osteoarthritis (Frobell et al. 2010, Grindem et al. 2011). In addition the cost of surgery and the subsequent rehabilitation following ACL reconstructive surgery is estimated to be around 25,000 US dollars per ACL injury case (de Loes e al. 2000). Moreover, Silvers and Mandelbaum (2007) reported an annual cost of around 2 billion dollars in the US.

1.6 Current surgical trends of ACL rupture

With the advancement in medical science, both anterior cruciate ligament reconstruction (ACLR) surgery and the subsequent rehabilitation have typically undergone considerable evolution over the last two decades. Factors such as extensive research in clinical settings and rehabilitative programmes and improved surgical techniques (improved arthroscopic procedures and fixation techniques) have contributed to the enhancement of better optimal outcomes following ACLR surgery (Mascarenhas et al. 2012, Aune et al. 2001). The surgical techniques of repairing the ruptured ACL and the use of a prosthetic ligament to replace the old ligament have recently fallen out of favour. This is due to the poor outcomes demonstrated by both techniques (Fu et al. 2000). Currently the two most common reconstructive surgical techniques for ACL ruptures are the bone- patellar -tendon-bone, the quadrupled semitendinosus/gracilis tendon using a biological autograft and/ or allograft materials in some cases (De Carlo and McDivitt 2006, Paessler and Mastrokalos 2003).

In addition it is believed that the strength of the bone- patellar -tendon-bone graft is 138-170 % stronger (load to failure 18000 to 2400 N) than the native ligament while for hamstrings the percentage is slightly lower (load to failure is around 1000 to 2500 N). Although BPTB graft seems to be the favourable choice of surgery as it continue to demonstrate better graft incorporation and stability (Fu et al. 2000, Biau et al. 2009), the hamstrings graft has however been reported to decrease harvest site morbidity with less post-operative complications (Mascarenhas et al. 2012).

To date, there is still no consensus as to whether one technique might have an upper hand or advantage over the other technique. Numerous studies have been carried out to assess the effectiveness of these two techniques (Aune et al. 2001, Fu et al. 2000, Freedman et al. 2003). Based on these studies, it is thought that the latter techniques, if combined with effective rehabilitation, have a very high success rate in post-reconstruction knee stability, activity levels and functional knee, and isokinetic muscle strength at 6 to 12 months postoperatively (Karasel et al. 2010, Risberg and Holm 2009). In a recent meta-analysis study of six randomized clinical trials, Biau et al. (2009) found that patients who had BPTB graft demonstrated more knee stability (adjusted odds ratio, 0.46; 95% confidence interval, 0.24-0.86; P =.016) than those who had hamstrings graft. The data included 423 patients who had symptomatic unilateral ACL injury and were randomly allocated to reconstruction with BPTB or hamstring tendon autograft (216 in BPTB group and 207 in hamstring group). Although ACL reconstructive (ACLR) surgery seems widely accepted as the preferred method of treatment for regaining joint stability within active individuals, there is still no consensus regarding the optimal postoperative rehabilitation programme. Therefore, in this chapter it is important to briefly discuss the influence of ACLR rehabilitation on achieving successful rehabilitation outcomes following ACLR.

1.7 Outcome measures of ACLR rehabilitation

Because of the enormous improvements in graft reconstruction techniques as a result of better understanding of the biology and biomechanics of knee joint, post-operative rehabilitation protocol has undergone considerable changes over the last two decades. Current rehabilitation programmes have become predominantly more aggressive by deploying a balance between the integration of the newly reconstructed graft and patient's desires for a safe and early return to his/her normal physical activities (Melegati et al. 2003). Therefore, ACLR rehabilitation plays a major role in determining the optimal clinical outcomes and patient satisfaction (De Carlo and McDivitt 2006). The systematic review (chapter two) will further discuss the issues related to accelerated rehabilitation following ACLR surgery.

Physiotherapists use outcome measures essentially to assess, evaluate and justify good clinical practice. There is strong evidence in the literature to suggest that there are deficits in the performance of knee following ACLR reconstructive surgery. These deficits include neuromuscular control, sensorimotor, functional and psycho-biological performances (Karasel et al. 2010, Cates and Cavanaugh 2009). Moreover, there is no consensus over the measures used to determine the readiness of physically active patients for a safe return to normal physical activities (Myer et al. 2006). For example, a study by Ardern et al. (2011) demonstrated that athletes had not been able to return to full competitive sporting activities following 12 months of ACLR rehabilitation. Therefore, any outcome measure that can accurately determine patient's physical and psycho-physiological status and subsequently evaluate patient's readiness to return to both daily activities as well as competitive sporting activities following ACLR rehabilitation would be of high benefit and merit. The three main categories of outcome measures deployed during ACLR rehabilitation are functional, objectives neuromuscular and subjective patient-reported outcome measures (Clark 2001, Karasel et al. 2010). With respect to subjective measures, a study by Kocher et al. (2004) found that it was largely due to the combination of subjective assessments (both symptomatic and functional) that determined patient satisfaction after ACLR surgery and rehabilitation. In addition, the assessment of patient commitment, depression, overall mood, and self-efficacy are vital in shaping and tailoring physiotherapy rehabilitation programme that will appropriately suit the individual physical tolerance as well as mental readiness in the early and advanced stages of ACLR rehabilitation and full recovery (Clark 2001). Some of the most commonly used questionnaires for knee symptoms and function include Lysholm Knee Rating System (Briggs et al. 2009, Brand and Nyland 2009), the International Knee Documentation Committee Subjective Knee Evaluation Form [IKDC] (Grindem et al. 2011, Gleeson et al. 2008), Knee injuries and Osteoarthritis Outcome Score [KOOS] (Ross and Lohmander 2003) and Knee Self Efficacy Scale [K-SES] (Thomee et al. 2010). On the other hand, objective measures should take into account the factor of injury prevention and knee dynamic stability. The commonly used objective neuromuscular measures following ACLR surgery and subsequent rehabilitation include range of motion (ROM), anterior tibial displacement (ATFD) for knee laxity, rate of force development (RFD), electromechanical delay (EMD,) sensorimotor performance (SMP), proprioception and isokinetic peak forces for hamstrings and quadriceps musculature while functional knee performance tests include hop (vertical, horizontal and triple), figure of eight, shuttle run and stair climbing tests. More details on the justification for the outcome measures selected for the studies of this thesis including their reliability and reproducibility had been offered in method section (chapter four).

2 Chapter Two: Accelerated Rehabilitation following Anterior Cruciate Ligament Reconstruction Surgery

(A Systematic Review of the Literature)

Abstract

***Objective*:** There is no consensus within the literature on the composition of accelerated rehabilitation for patients who have undergone ACL reconstructive (ACLR) surgery. This review aims to examine the effects of increased exercise-related stress (i.e. dosage of frequency, intensity and time) associated with introducing early weight bearing, range of motion and neuromuscular conditionings in the accelerated rehabilitation of ACLR using objective and patient-reported outcome measures. It also contemplates the clinical implications of the latter discriminators of changes in performance as determinants of successful ACLR rehabilitation.

Design/Method: A systematic review was undertaken from February 2013 to May 2014. The search strategy of this systematic review adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and included the electronic database search of Medline, CINAHL, and SPORTDiscus using EBSCOHost search engines to identify the relevant studies. The methodological quality of this review was assessed using specific criteria that included, Pedro scaling, enhanced inclusion criteria, the prospective reviewers and randomised controlled trials (RCTs). The search keywords included accelerated, rehabilitation, exercise therapy, anterior cruciate ligament and ACL.

***Results/Conclusion*:** Ten RCTs were identified by the systematic review. Five out of ten systematic reviews investigating the effectiveness of accelerated rehabilitation demonstrated moderate effect sizes (mean relative effect sizes [Cohen's d = 0.33 (ranging from 0.1 to 1.64) in terms of improved knee laxity, neuromuscular performance, ROM restoration and patient self-reported outcome measures. In addition, the means of number of sessions/week, sets, weight, time and period of intervention were 3, 3, 70% repetition maximum (RM), 30 minutes and 7.25 weeks, respectively, for the accelerated studies included in this review. However, there is still a need for further robust studies on the quantification of the exercise associated with accelerated rehabilitation and their effects on the outcomes measures of patients who underwent ACLR rehabilitation.

2.1 Introduction

The vast majority of active individuals who sustain complete rupture of ACL have the preference of choosing reconstructive surgery over conservative treatment as surgery offers more stability for the knee joint than conservative treatment in the physically demanding activities (Shaw et al. 2005). The main objective of any rehabilitation of ACLR surgery is to primarily re-establish knee functional capability and eliminate pain (Shelbourne et al. 2006, Shaw et al. 2005, Beynnon et al. 2011).

Accelerated rehabilitation is a programme that offers a structured physical conditioning protocol similar to the current standardised programme (6-9 months period) but in which clinical rehabilitation milestones are achieved earlier [4-6 months period after ACLR surgery] (Van Grinsven et al. 2010, Shaw 2002, Silva et al. 2012, De Carlo et al. 1997). The latter authors had advocated accelerated rehabilitation based on their previous work which demonstrated that exercises causing significant strain to ACL could be introduced earlier in the accelerated programme while the same exercises could be delayed in the non-accelerated program. Additionally both rehabilitation programmes would receive no delay in the exercises that did not cause significant ACL strain in the early of phase of ACLR rehabilitation programme.

It has been demonstrated that accelerated rehabilitation programmes have the advantage over the long traditional programme (6-9 months) with the former demonstrating less rehabilitation time, less cost, earlier return to full range of motion (ROM), increased muscle strength and knee function (Shaw 2002). The systematic review of Van Grinsven et al. (2010) have shown that accelerated rehabilitation improved the components of neuromuscular control (Risberg et al. 2007), open and closed kinetic chain performances (Tagesson et al. 2008) and thigh muscle strengths (Risberg and Holm 2009) which were considered as significant contributors to the effectiveness of a successful ACLR rehabilitation. However, there is still a gap in the literature on robust randomised control trials focusing on the frequency, intensity and time (FIT) of exercise conditioning during the early, middle and late phases in order to achieve optimal and successful outcomes.

This review aims to systematically examine the evidence concerning the effects of increased neuromuscular exercise stress (i.e. increased dosage) associated with introducing early weight bearing, range of motion, muscular strength and proprioceptive conditionings on objective and patient-reported outcome measures during ACLR accelerated rehabilitation. The review will also quantify the dosage of the accelerated rehabilitation in order to determine the optimal overall dose-response required for successful ACLR rehabilitation. It is hoped that this review will establish a platform for providing the best evidence available from the contemporary literature (2003-2013) with regard to accelerated rehabilitation of ACLR surgery. The main focus in the current literature has shifted from a comparison between ACLR rehabilitation protocols in terms of duration of rehabilitation only (i.e. 6 versus 9 months) to a comparison between treatments in terms of the effects of timing (i.e. early versus late) and volume (intensity and frequency) of exercise conditioning prescribed in the rehabilitation protocols (Karasel et al. 2010, Shaw 2002, Wright et al. 2008).

2.2 Method

The primary focus of the systematic review was to compare between ACLR rehabilitation programmes (4-6 months) in terms of increased neuromuscular exercise stress (increased dosage) conditioning on objective and patient self-reported outcome measures. A systematic review was undertaken from February 2013 to May 2014.Only randomised controlled trial studies were eligible for the review. Participants suffering with systemic diseases such as rheumatoid arthritis, kidney failure, and heart or lung disease were not included as these participants are likely to possess different baseline performance capabilities, and might exhibit differential performance adaptations and are subsequently not representative and relevant to the tested participants of this review. The inclusion and exclusion criteria for the review are summarised below:

2.2.1 Inclusion criteria:

- Population: male and or female over the age of 16 years.
- Comparison/ Intervention: studies of accelerated rehabilitation with neuromuscular outcome measures versus contemporary rehabilitation programmes.
- Results: functional and neuromuscular outcomes.
- Study design: randomised controlled trials.
- Surgery: ACL reconstruction with a BPTB or semitendinosus graft (ST/G)
- Duration: intervention group having accelerated rehabilitation programme for less than 6 months.
- Search time period: 2003- 2014.
- Language: English written articles.

2.2.2 Included physical therapy interventions:

Exercise was included if it included the following neuromuscular trainings:

- Quadriceps and hamstring muscle strengthening using the following movement characteristics:
  Isometric/isotonic/isokinetic
  Concentric/eccentric

Open kinetic chain/closed kinetic chain

- Joint mobility:

  Active

  Active assisted

  Resisted

- Gait re-education
- Neuromuscular function/balance and proprioception

2.2.3 Exclusion criteria:

- Population: participants suffering from any clinical systemic disease, (e.g. rheumatoid arthritis, chronic obstructive airway disease or heat disease, etc.) or animal studies.
- Results: studies with only endurance outcomes or chemical and or cellular outcomes only.
- Surgery: synthetic grafts.
- Study design: articles were excluded if only the abstract was available and not the full text. However reviews and meta-analyses were read to provide the enough evidence in the literature and discussion.
- Duration: control group having rehabilitation programme for not less than 4 months.

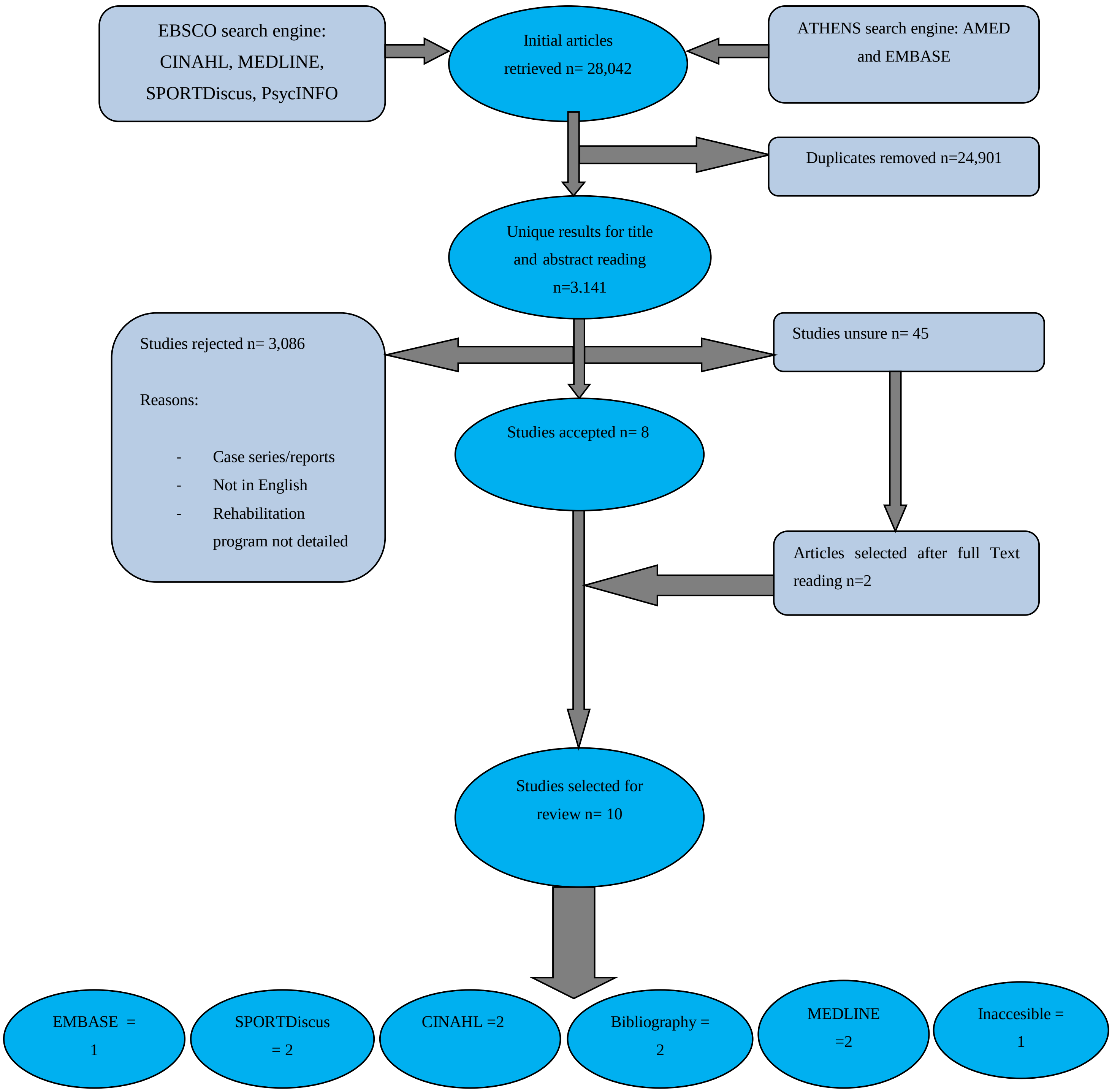
2.2.4 Excluded physical therapy interventions:

- The use of hydrotherapy in the acute phase of rehabilitation.
- Electrotherapy modes including interferential therapy, laser therapy, ultrasound and/or any other modes for pain and swelling relief.
- Complimentary therapies (Chinese acupuncture, osteopathy, reflexology etc.)

Table 2.1 Overview of the keywords and the combination used for the review.

	Keywords	Combination	Final Combination
Subjects	Clinical population undergoing ACL reconstruction and rehabilitation		
Condition	1) ACL 2) anterior cruciate ligament	7) 1 AND 2	
Intervention	3) Accelerated 4) Rehabilitation 5) Exercise therapy	8) 3 AND 4 AND 5	
Level of Evidence	6) RCT	9) 6	
Condition AND Intervention AND Level of Evidence			7 AND 8 AND 9

Figure 2.1 Flow chart on the selection process of the studies for the review



2.2.5 Search strategy

Computer searches utilising EBSCO and Athens via Queen Margaret University and NHS Evidence via RJAH Orthopaedic and District NHS Foundation Trust were performed. The search terms used in all of the data bases were ACL OR anterior cruciate ligament AND accelerated OR rehabilitation OR exercise therapy AND RCT. Table 2.1 shows a summary of keywords used in this review.

2.2.6 Data extraction

A schematic representation of the study selection process is presented in Figure 2.1. Exclusion of studies with irrelevant content was carried out in three steps. Firstly, two independent reviewers performed the literature search. All the relevant titles were selected first from the list obtained from the electronic database searches. Each reviewer examined publications fulfilling the inclusion criteria. The duplicates of these articles were removed and then the title and abstracts of the remaining studies were considered based on the inclusion and exclusion criteria mentioned above. Some studies were excluded because neither the outcome measures nor the interventions were consistent with the inclusion criteria of this review. Secondly, the reviewers divided the studies into three categories; "reject", "unsure" and "accept". The full paper of all the abstracts labelled as "unsure" and "accept" were read first. This procedure was followed so as to avoid the rejection of any useful articles. The studies in the "reject" category were excluded because the outcome measures were other than functional and neuromuscular outcomes. Thirdly, the reference lists of relevant articles were searched manually in an attempt to identify further additional articles that were not originally identified in the database search. This procedure resulted in a further thee research articles for inclusion in the review that had not been discovered by the original literature search methods of EBSCO and Athens. Consensus was used in the final outcome of this systematic review to resolve any disagreements between the two reviewers. If consensus was not reached, a third reviewer would be involved for final decision.

2.2.7 Effect size calculation

Where possible Cohen's *d* effect size was calculated using pooled standard deviations (SD) for each study ([post-test mean-pre-test mean] ÷ pooled SD). However some studies did not provide absolute mean data, standard deviations or standard errors within the text of the article for all or some of the outcomes. Some articles did not specify whether standard deviation or standard error was used, therefore an assumption was made in these instances. The *d* values were calculated for neuromuscular outcomes if they were statistically significant according to the author. If the outcome was not significant the *d* value was only calculated if it served as a comparison to the significant finding. A *d* value of less than 0.4 represented a small magnitude of change (effect size) while 0.41–0.7 and greater than 0.7 represented moderate and large effect sizes respectively (Thomas and Nelson 2001). Table 2.4 offers an overview of the relative effect sizes (Cohen *d*) of the studies included within this review

2.2.8 Quality rating scale

The studies selected for the systematic search were evaluated for the quality of methodology using the PEDro (Physiotherapy Evidence Database) rating scale. This rating scale was chosen due to its reliability and wide use in presentations and programmes on evidence-based health care practice (Maher et al. 2003). The PEDro scale is an ordinal scale consisting of eleven items which include: eligibility criteria specification; random allocation of subjects to groups; concealed allocation; groups similar at baseline; blinding of subjects, therapists and assessors; obtaining outcome measures from more than 85% of subjects; intention-to-treat analysis; reporting of results of between-group statistical comparisons; point measures and measures of variability. Since the eligibility criteria specification is an external validity criterion, it is not included in the total scoring. Therefore, the PEDro scale is rated between 0-10 (Herbert et al. 1998). Table 2.3 offers PEDro ratings for the studies included in this review.

2.3 Results

The search from EBSCO and Athens search engines identified a total of 28,042 articles. Duplicates were filtered electronically where possible then performed manually (24,901). Abstracts of the unique results (3,141) were read for possible inclusion in the review. At this point the search was refined to "reject", "unsure" and "accept" based on the titles and the abstracts where necessary. Of the 3,141 articles, 8 were accepted on the basis of titles and abstracts, and 3,096 articles were rejected because they were not RCTs, not in English language and not detailing the contents of the rehabilitation protocols following ACLR surgery. Of the 45 "unsure" articles, 2 were included in the review making it a total of 10 articles for the final review (1 inaccessible).

Table 2.2: A summary of the studies included in the systematic review.

	Author, Year	Subjects, Surgery	Follow-up period	Rehabilitation Period	Training Interventions	Intervention Period	Training Intensity & Frequency	Compliance	Outcome Measures	Results
1	Beynnon et al. (2005)	25, BPTB	Pre, 3, 6, 12, and 24 and 48 months	Accelerated 19 weeks, non-accelerated 32 weeks	Exercises causing ACL strain were started earlier in the accelerated and delayed in non-accelerated.	First 12 weeks after surgery	3 times/week for 19 weeks for accelerated, and 32 weeks for non-accelerated. No intensity and frequency of exercises given.	Accelerated: 68, Non accelerated: 40	IKDC, KT1000, KOOS, single leg hop test	Both groups were similar in terms of clinical assessment, patient satisfaction, activity level, function, increased knee laxity and response of the biomarkers
2	Beynnon et al. (2011)	42, BPTB	Pre, 3, 6, 12, and 24 and 48 months	Accelerated 19 weeks, non-accelerated 32 weeks	Exercises causing ACL strain were started earlier in the accelerated and delayed in non-accelerated.	First 12 weeks after surgery	3 times/week for 19 weeks for accelerated, and for 32 weeks for non-accelerated. No intensity details given.	Accelerated: 94, Non accelerated: 53	IKDC, KT1000, KOOS, leg hop and thigh isokinetic strength, Tegner activity level	Groups similar in clinical assessment, functional performance, proprioception, increased knee laxity, isokinetic thigh muscle strength but KOOS assessment of quality of life did not return to pre=injury levels. Significant improvement in thigh muscle strength at 3-month follow-up in accelerated compared with non-accelerated
3	Risberg & Holm (2009)	74, BPTB	Pre, 6,12, 24 months	NE & SE: 6 months	NE: balance, dynamic joint stability, plyometric & agility exercises. SE: quads, hamstrings, gluteus medius & gastrocnemius	NE; 6 phases (3 to 5 weeks each). SE; 4 phases (2 to 8 weeks each).	2-3 times/week for 6 months. SE: 3 sets (8 to 12 repetitions) at 50% to 80% 1RM, at phase 4, 3 sets (6 to 8 repetitions)	NE: 71, SE: 91	Cincinnati knee score, VAS, Knee ROM, isokinetic muscle strength, single-legged hop tests, SF-36, KT-1000	2 years after ACLR, no significant differences between the 2 programs in Cincinnati knee score, significantly improved knee global function, reduced pain for NE group compared with SE & significantly improved hamstring strength for SE.

Table 2.2: A summary of the studies included in the systematic review.

4	Risberg et al. (2007)	74, BPTB	Pre, 3 and 6months	NT & ST: 6 months	NT: static and dynamic balance & perturbation exercises. ST: all lower extremity exercises.	NT; 6 phases (3 to 5 weeks each), ST; 4 phases.	2-3 times/week for 6 months. ST: 3 sets (8 to 12 repetitions) at 50% to 80% 1RM, at phase 4, 3 sets (6 to 8 repetitions)	NE: 71, SE: 91	Cincinnati Knee Score, VAS, single leg hop test, SF-36, isokinetic muscle strength	Significantly improved Cincinnati Knee Scores and VAS scores for global knee function in NT compared with the ST at 6-month follow up. No significant differences between groups for outcome measures of hop, balance, proprioception and isokinetic muscle strength.
5	Liu-Ambrose et al. (2003)	10, Hamstring	Pre, 6 and 12 weeks	PT & ST: 6 months	PT: balance, agility and perturbation exercises. ST: OKC for quads & hams	First 12 weeks after surgery	3 times/week. ST progression: graduated weight resisted exercise increase.PT progression: decreasing base of support and stability surface.	ST; Mean 32 ± 3, PT; Mean 31 ± 2 sessions.	Peak torque time, concentric and eccentric torque quadriceps/hamstring (N.m), single leg hop test, Tegner and Lysholm	Significant group by time interaction for peak torque time. PT group with greater %change in isokinetic strength, similar significant gain in functional ability and subjective scores
6	Heijne & Werner (2007)	68, BPTB & Hamstring	Pre, 3, 5 and 7 months	All subgroups: 4-6 months	4 groups; BPTB (P4; after 4 weeks) or (P12; after 12 weeks) of OKC quadriceps exercises. Hamstring (H4; after 4 weeks) or (H12; after 12 weeks) of quads OKC exercises.	From 4th and 12th weeks after surgery.	2-3 times/week for 4-6 months. No intensity and frequency of exercises details given.	Not assessed.	ROM, KT-1000, postural sway (KAT 2000), thigh muscle torques (Kin–Com dynamometer) and anterior knee pain score	Significant differences in trends (changes over time) were found when comparing the four groups, for both quadriceps muscle torques ($P < 0.001$) and hamstring muscle torques ($P < 0.001$).Early introduction of OKC exercises for quadriceps did not influence quadriceps muscle torques neither in patients operated

Table 2.2: A summary of the studies included in the systematic review.

										on patellar tendon nor hamstring grafts.
7	Tagesson et al. (2008)	42, BPTB & Hamstring	4 months post-surgery	16 weeks	CKC: squatting, OKC: seated knee extension.	From week 5 -16 (11 weeks).	3 times/week (3 sets* 10 repetitions; 50-60% 1RM then increased by 10% at weeks 11 and 15).	35 sessions (CKC) and 33 sessions (OKC)	Dynamic tibial translation, muscle strength, jump performance, muscle activation, Lysholm score and KOOS	No group differences in dynamic translation, OKC group had significantly greater isokinetic quadriceps strength but hamstring strength, performance on the 1-repetitionmaximum squat test, muscle activation, jump performance, and functional outcome did not differ between groups.
8	Perry et al. (2007)	49, BPTB & Hamstring	8 and 14 weeks	CKC & OKC: 6 months	CKC: unilateral training of hip & knee extensors on leg press machine. OKC: unilateral knee extension (ankle weights or hamstring curl machine)	6 week intervention (from week 8-14 after ACLR)	3 imes/week for 6 weeks. Week 1-4; 3 sets of 20 RM. Week 4-6; 3 sets of 6 RM.	Not assessed.	Arthrometer and function with the Hughston Clinic knee self-assessment questionnaire, single leg hop test.	No statistically significant (one-way ANOVA,p>0.05) differences were found between the treatment groups in knee laxity or leg function.
9	Shaw et al. (2005)	91, BPTB & Hamstring	Day one, 2 weeks,1, 3 and 6 months	Quads & No Quad exercises: 6 months	Quads group; straight leg raises and isometric quadriceps. No quad group; did not do these execs.	First 2 weeks after surgery	10 repetitions* 3 times/daily	No difference between groups in adherence	Quadriceps lag, functional hop testing, isokinetic quadriceps strength, Cincinnati scores, knee laxity	Quads group significantly improved knee ROM. No significant differences between two groups for quads lag, functional hop, isokinetic quads and Cincinnati. Laxity not significantly different in treatment groups over time

Table 2.2: A summary of the studies included in the systematic review.

10	Cooper et al. (2005)	29, not specified	Pre pre-operative and 6 weeks	PT & ST: 6 months	PT: wobble boards, mini trampolines, balance discs & exercise balls. ST: bike, leg press, double squat, bridging.	First 6 weeks after surgery	20-40 minutes for ST: 3 - 4 sets of 10 to 15 repetitions (load increased in later phases), and for PT.	10 sessions attended for both ST and PT	Cincinnati knee rating system, single leg hop, ROM	No difference between the two forms of exercise and strength training may be more beneficial than proprioceptive and balance training in the early phase of rehabilitation after ACL

<u>Summary and Keys:</u>

ACLR, Anterior Cruciate Ligament Reconstruction

BPTB: Bone-Patellar-Tendon-Bone

IKDC: International Knee Documentation Committee

KOOS: Knee Osteoarthritis Outcome Score

KT1000: Knee laxity arthrometer test

WBVT: Whole-Body Vibration Therapy

RM: Repetition maximum

HHD: Heel Level Difference

OKC: Open Kinetic Chain

ROM: Range Of Motion

NE: Neuromuscular Exercise

SE: Strength Exercise

VAS: Visual Analogue Scale

SF-36:health-related measurement of quality of life

P4:4th week post -surgery, P12: 12 weeks post- surgery

H4: 4th week post-surgery, H12: 12th weeks post- surgery

NT: Neuromuscular Training

ST: Strength Training. PT: proprioceptive training.

Table 2.3: PEDro scores of the studies included in the systematic review.

	Author, Year	Pedro Scale 1	2	3	4	5	6	7	8	9	10	11
1	Beynnon et al. (2005)	Yes	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Yes
2	Beynnon et al. (2011)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
3	Heijne & Werner (2007)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
4	Risberg & Holm (2009)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
5	Liu-Ambrose et al. (2003)	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes
6	Tagesson et al. (2008)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
7	Risberg et al. (2007)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
8	Perry et al. (2007)	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
9	Shaw et al. (2005)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
10	Cooper et al. (2005)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes

PEDro Scale:

1 eligibility criteria were specified
2 subjects were randomly allocated to groups
3 allocation was concealed
4 the groups were similar at baseline
5 there was blinding of all subjects
6 there was blinding of all therapists
7 there was blinding of all assessors
8 measures of at least one key outcome were obtained from more than 85%of the subjects
9 subjects for whom outcome measures were available received the treatment or control condition
10 results of between-group statistical comparisons are reported
11 the study provides both point measures and measures of variability

Table 2.4 Overview of the relative effect sizes (Cohen *d*) of the studies included in the review

Studies	Outcome measures	Item	Groups	$mean_1$	sd_1	$mean_2$	sd_2	Cohen *d*
Beynnon et al. 2005	KT-1000 (90 N)	(90 N) KT-1000 (mm)	Accelerated	1.1	2.2	2.2	2.0	
			Non-accelerated	-0.8	1.9	1.8	2.2	0.19
	KOOS	Pain	Accelerated	75.6	12.9	93.9	8.7	
			Non-accelerated	82.1	13.6	94.1	5.7	0.01
		Symptoms	Accelerated	73.8	12.8	94.2	5.5	
			Non-accelerated	78.1	18.8	88.2	13.6	1.38
		ADL	Accelerated	87.5	6.3	97.6	3.1	
			Non-accelerated	87.6	14.9	98.8	2.4	0.01
		Sport, Recreation	Accelerated	46.0	17.1	85.0	12.5	
			Non-accelerated	52.7	21.8	86.3	12.8	0.09
		Quality of life	Accelerated	38.2	12.3	78.7	11.1	
			Non-accelerated	35.8	19.8	82.4	17.3	0.36
Beynnon et al. 2011	KOOS	Pain	Accelerated	78.0	14.0	93.0	12.0	
			Non-accelerated	77.0	15.0	95.0	6.0	0.22
		Symptoms	Accelerated	67.0	19.0	93.0	6.0	
			Non-accelerated	68.0	22.0	90.0	12.0	0.32
		ADL	Accelerated	88.0	13.0	97.0	10.0	
			Non-accelerated	86.0	14.0	98.0	3.0	0.14
		Sport, Recreation	Accelerated	57.0	28.0	92.0	17.0	
			Non-accelerated	60.0	31.0	93.0	9.0	0.08
		Quality of life	Accelerated	40.0	19.0	86.0	14.0	
			Non-accelerated	36.0	27.0	80.0	18.0	0.38
		Laxity AP displacement (mm)	Accelerated	8.30	4.47	11.50	4.99	
			Non-accelerated	8.3	4.73	12.80	5.31	0.26
Risberg & Holm 2009		KT-1000, mm	SE	7.90	3.60	3.00	2.70	
			NE	7.20	4.30	4.00	2.90	0.36
		Global function (VAS), mm	SE	33.9	25.3	71.8	25.3	
			NE	39.10	25.50	82.00	23.40	0.43
		One-legged hop %	SE	93.70	11.30	93.90	12.50	
			NE	90.10	15.50	94.00	10.10	0.01
	Isokinetic, %	Flexion at 60 %	SE	80.60	19.50	92.00	13.90	
		Flexion at 60 %	NE	86.80	24.20	91.50	18.90	0.03
		Extension at 60 %	SE	79.00	18.00	88.50	14.10	
		Extension at 60 %	NE	79.40	20.60	90.10	13.90	0.12
Risberg et al. 2007		KT-1000 (mm difference)	ST	7.90	3.60	3.00	2.90	
			NT	7.20	4.30	3.40	2.60	0.15
		Cincinnati Knee Score	ST	65.30	13.00	73.40	9.60	
			NT	65.20	17.00	80.50	12.30	0.66
		VAS pain-activity-(mm)	ST	35.40	23.30	24.60	20.30	
			NT	35.20	26.50	20.70	21.00	0.19

		VAS for knee function (mm)	ST	33.90	25.30	59.30	23.10	
			NT	39.10	25.50	72.40	22.10	0.59
		One-leg hop test (%)	ST	93.70	11.30	81.00	18.20	
			NT	90.10	15.50	84.90	10.90	0.27
	Isokinetic, %	Flexion total work 60/s (%)	ST	80.60	19.50	88.30	14.40	
			NT	82.90	20.40	86.30	14.30	0.22
		Extension total work 60/s (%)	ST	79.00	18.00	67.30	16.10	
			NT	79.40	20.60	79.10	17.10	0.73
Liu-Ambrose et al. 2003		Concentric quadriceps (N.m)	ST	144.40	31.40	141.80	20.17	1.21
			PT	80.00	32.80	107.36	36.46	
		Eccentric quadriceps	ST	161.00	38.22	158.42	17.10	0.38
			PT	79.60	29.00	127.36	121.65	
		Concentric hamstring	ST	71.00	24.60	75.83	31.95	0.42
			PT	53.20	15.50	61.71	35.49	
		Eccentric hamstring	ST	85.40	28.30	87.02	20.33	0.50
			PT	58.60	17.20	73.31	37.27	
		Single leg hop (cm)	ST	160.30	33.80	193.48	24.69	1.64
			PT	133.30	38.30	156.76	22.59	
Tagesson et al. 2008	Lachman 90-N	Injured	CKC	6.30	2.10	6.10	1.70	0.09
			OKC	5.90	1.50	6.10	1.90	
	Lachman 134-N		CKC	7.80	2.50	7.80	2.40	
			OKC	7.70	1.50	7.60	2.10	0.09
Perry et al. 2007		Injured ATD (mm)	CKC	12.00	2.00	12.00	3.00	
			OKC	11.00	3.00	12.00	3.00	0.00
		Hughston Clinic Questionnaire	CKC	42.00	12.00	32.00	13.00	
			OKC	38.00	13.00	29.00	13.00	0.24
Shaw et al. 2005		Flexion ROM (degrees)	No quads	77.10	21.60	142.60	7.60	
			Quads	73.80	20.30	141.60	6.90	0.14
		Extension ROM (degrees)	No quads	22.40	7.90	4.90	4.20	
			Quads	22.50	8.00	5.70	4.10	0.20
		VAS Pain at rest (mm)	No quads	2.60	2.00	0.30	0.60	
			Quads	3.10	2.20	0.30	0.60	0.00
		VAS Pain on execs (mm)	No quads	6.00	2.10	2.10	1.80	
			Quads	6.90	2.00	2.00	1.90	0.06
		CKRS Symptoms	No quads	4.80	1.00	6.80	1.10	
			Quads	4.90	1.00	7.50	1.20	0.62
		CKRS Patient grade	No quads	4.50	0.80	6.70	1.40	
			Quads	4.50	1.10	7.10	1.60	0.27
		CKRS Sports activity	No quads	55.10	26.60	75.80	16.00	
			Quads	49.10	21.30	79.30	13.40	1.49
		CKRS ADL Function	No quads	23.60	8.50	33.90	5.90	
			Quads	25.90	6.30	35.30	3.70	0.29
		CKRS Sports Function	No quads	40.70	2.90	73.00	12.90	
			Quads	42.20	6.20	76.30	14.60	0.24
Cooper et al. 2005		Cincinnati	Pain - Balance	6	2.00	6.50	2.30	

knee rating system	Pain - Strength	4.00	0.00	6.00	1.00	0.29
	Swelling – Balance	6.00	2.00	7.50	2.00	
	Swelling – Strength	4.00	4.00	8.00	2.00	0.26
Overall condition	Balance	5.00	1.00	6.50	1.30	
Overall condition	Strength	4.00	1.00	7.00	2.00	0.30
Walking	Balance	30.00	10.00	40.00	10.00	
Walking	Strength	30.00	0.00	40.00	0.00	0.00
Stairs	Balance	30.00	2.50	40.00	10.00	
Stairs	Strength	30.00	0.00	40.00	10.00	0.00
Squatting	Balance	30.00	10.00	30.00	0.00	
Squatting	Strength	20.00	30.00	30.00	0.00	0.00
Knee flexion	Balance	132.10	7.10	133.90	7.00	
	Strength	125.10	2.60	129.40	5.00	0.76
Knee extension	Balance	0.71	1.76	0.10	1.70	
	Strength	0.58	1.11	-0.10	1.70	0.00
					Total *d*	16.714
					Mean *d*	0.33

Keys:

CKC: Closed kinetic chain

OKC: Open kinetic chain

SE: Strength Exercise

ST: Strength training

NT: Neuromuscular training

NE: Neuromuscular exercise

CKRS: Cincinnati Knee Rating Score

QE: Quadriceps exercise

2.4 Discussion

The discussion of the articles included in this review is divided into the following five subtitles: 1) weight bearing, knee brace and OKC versus CKC exercises, 2) proprioceptive training versus strength training 3) intensity of training and patient's compliance, 4) clinical implications and 5) limitations of the review.

2.4.1 Weight bearing, knee brace and OKC versus CKC exercises

Three of the total 10 articles in this review defined accelerated rehabilitation on the basis of duration and early introduction of neuromuscular conditionings (Beynnon et al. 2005, Beynnon et al. 2011, Tagesson et al. (2008). A 19 weeks accelerated rehabilitation group versus 32 weeks non - accelerated rehabilitation group was investigated in the work of Beynnon et al. (2005). With a PEDro scale of 7/10, Beynnon and colleagues introduced exercises of increased ACL strain earlier to the 19 weeks group compared to the non-accelerated group. The latter exercises include earlier increased ROM, weight bearing, weaning from brace and OKC for quadriceps. The results found there was no difference in the increase of anterior knee laxity relative to the baseline values between the 2 groups. Similarly the study showed no group difference in terms of clinical assessment, activity level, functions and patient satisfaction (represented in KOOS; Knee Osteoarthritis Outcome Score). There were no significant group differences found for the KOOS outcomes of pain, activities of daily living, sports and recreation participation and knee-related quality of life for accelerated and non-accelerated rehabilitation groups, respectively). Summaries of studies of this review with their effect sizes (Cohen *d*) are offered in Table 2.4.

In a similar study design and treatment intervention, Beynnon et al. (2011), PEDro scale 9/10, demonstrated that both accelerated (19 weeks) and non-accelerated (32 weeks) groups were similar in terms of increased knee laxity, clinical assessment, patient satisfaction, function, proprioception, and isokinetic thigh muscle strengths at the two years follow up after ACLR surgery. With regards to increased anterior knee laxity relative to immediately after surgery values, no significant difference was observed between the two groups (d = 0.26), and no difference in KOOS outcomes of pain, symptoms, activities of daily living, sports and recreation participation and knee-related quality of life (d = 0.34, 0.32, 0.14, 0.08 and 0.38 respectively) for accelerated and non-accelerated rehabilitation groups. Although this study had thigh muscle (quadriceps and hamstrings) isokinetic strengths and single leg hop tests as the main outcome measures, it was however not possible to obtain their values and therefore

Cohen's *d* calculation based on the graphs and figures presented within the article was not possible.

In a 16 weeks rehabilitation programme, Tagesson et al. (2008), PEDro scale 8/10, examined the effects of closed kinetic chain (CKC) versus open kinetic chain (OKC) exercises during ACLR rehabilitation. Tagessson and colleagues divided participants into two groups; one was instructed to perform OKC exercises while the CKC exercises were instructed to the other group. For patients in the CKC group, squatting on 1 leg was the primary strengthening exercise for quadriceps while for patients in the OKC group, seated knee extension on 1 leg was considered as the primary strengthening exercise for quadriceps. Both exercises were initially introduced with low load (50-60% repetition maximum (RM) from phase 2 (week 5-8 postoperatively) of rehabilitation programme. Gradual increase of load was then allowed using the uninjured leg as a reference point for determining the loads on the injured leg. The study's results demonstrated that OKC group had significantly greater isokinetic quadriceps strength although no values were offered in this study to calculate the effect sizes. However, hamstring strength, performance on the 1RM squat test, muscle activation, jump performance, functional outcome did not differ between the groups.

On the other hand, Heijne and Werner (2007), PEDro scale 7/10, investigated the influence of OKC and CKC exercises on the physical outcomes of 6 months rehabilitation after ACLR surgery (Bone-patellar-tendon-bone (BPTB) and hamstrings reconstructive surgeries). The study randomly allocated participants into 4 subgroups; early start (P4) or late start (P12) of OKC quadriceps exercises for those who went for BPTB reconstruction, and early start (H4) or late start (H12) of quadriceps OKC exercises for those who went for Hamstring tendon reconstruction. There were no significant group differences with respect to ROM at 3, 5 and 7 months postoperatively. Another finding of this study was that early start of OKC exercises of quadriceps in patients who had BPTB graft did not differ from those with late start of OKC exercises with regards to anterior knee laxity. The study concluded that early start of OKC quadriceps exercises after hamstring graft resulted in significantly increased anterior knee laxity when compared to late start and with early and late start after BPTB graft. The authors concluded that introducing quadriceps OKC exercises earlier did not influence quadriceps muscle torques in both patients of BPTB and hamstring grafts, suggesting that it is rather the type of graft and not the type of exercises that determines the strength of the latter muscle. However, it might be argued that the latter study had the patients training isotonically in a normal leg extension machine (i.e. with decreased knee flexion, the external torque increases). This type of training causes lower resistance of the quadriceps muscle in the knee angles where the muscle is stronger, making quadriceps strength training less effective compared with isokinetic training as used in the study of Tagessoon et al. (2008). Unfortunately no relative effect size calculations of the main outcome measures could be established from the study of Heijne and Werner (2007), as only confidence interval (instead of standard deviation) and percentage changes were referred to within the tables of this study.

In another RCT study, Perry et al. (2007), PEDro scale 7/10, examined a group who underwent a 6 weeks programme of CKC knee extensors on leg press machine and a group who performed OKC knee extensor training during the middle phase of rehabilitation. There was no statistically significant ($p>0.05$) difference found between the treatment groups in knee laxity or leg function.

Finally, based on the 6 months rehabilitation programmme, Shaw et al. (2005), PEDro scale 8/10, investigated the effects of introducing straight leg raise and isometric quadriceps exercises in one group and compared it to a group who did no quadriceps exercises in the first two weeks of ACLR rehabilitation. Study results revealed that quadriceps exercises significantly improved knee flexion and extension ROM. However, no significant difference was found between the two groups for quadriceps lag, functional hop testing, isokinetic quadriceps strength and knee laxity over time. However patients in quadriceps group demonstrated significantly more favourable Cincinnati scores for symptoms (d= 0.62) and problems with sport (d= 1.49). Shaw and colleagues concluded that isometric straight leg raises and quadriceps exercises can be prescribed safely during the first two postoperative weeks and offer advantages for quicker recovery of ROM and knee stability.

2.4.2 Neuromuscular versus strength training

Four studies (Risberg and Holm 2009, Risberg et al. 2007, Liu-Ambrose et al. 2003, Cooper et al. 2005) had examined muscular strength versus neuromuscular (proprioceptive) training effects on the outcomes of ACLR rehabilitation. Risberg et al. (2007), PEDro 7/10, investigated the effects of 6-month neuromuscular training (NT) against a traditional strength training (ST) in ACLR surgery rehabilitation. Briefly both programmes offered different exercises at the early stages of the rehabilitation. For instance, the ST group had early knee extension ROM in the period 1-2 weeks postoperatively while the latter exercise had been offered 1-2 weeks postoperatively for the NT group. Squatting exercises without bars/weights was started in 5 - 8 weeks postoperatively in ST, while in NT group the exercise was started 9 weeks postoperatively. The results demonstrated that NT group significantly improved Cincinnati Knee Scores and visual analogue scale (VAS) scores for global knee function compared with the ST group at the 6-month follow-up. The magnitude of the treatment effect for the NT group indicated a moderate change in subject -reported (i.e. Cincinnati Knee Scores and VAS) knee function compared with the ST group (*d* = 0.66). However similar improvements between the groups were observed for the outcome measures of single leg hop, balance, proprioception, and muscle strength tests.

Risberg and Holm (2009), PEDro scale 7/10, on the other hand examined the effects of two treatments groups; group 1) neuromuscular training versus group 2) strength training on the outcomes of 6 months ACLR rehabilitation. The intervention for NE training was based on 6 phases of 3 to 5 weeks each while the SE consisted of 4 phases. There were no significant differences between the NE and SE programmes 1 and 2 years after ACLR surgery for the primary outcome measurement (Cincinnati knee score). However, *d* values could not be obtained due to absence of means and standard deviation values of the two groups in this study. There were, nevertheless, significantly improved global knee function (*d* = 0.43) and reduced pain during activity for the NE group, compared with the SE group, and significantly improved hamstring muscle strength (*d* = 0.22) for the SE group compared with the NE group, 2 years after ACL reconstruction. Given that this study had a longer follow up (2 years) compared to the 1 year follow up in the study of Risberg et al. (2007), obtaining better rehabilitation outcomes appear to take longer than one year period.

In a similar study, a comparison between proprioceptive training (PT) groups against a strength training (ST) group), Liu-Ambrose et al. (2003), PEDro scale 6/10, found significant group by time interaction for peak torque time, greater percentage change in isokinetic strength in ST group (*d* =1.2) than PT, but both groups had similar significant gain in knee functional ability and subjective scores. He concluded that quadriceps strength was the sole predictor for functional ability (single leg hop test), with a coefficient of determination of 0.72 and accounting for 72% of the variance observed, and that PT training could obtain isokinetic strength gain if acting alone. However, the study used percentage difference for comparing the isokinetic torques as the baseline differences between the two groups were significant. Moreover, the study had small sample size (10 participants) therefore did not have sufficient power to detect the difference hypothesized (10-12% between the two groups) in secondary outcomes including Lysholm scores, hop tests and isokinetic strength. It could be argued that the discrepancy in waiting time (12 versus 7 months) observed between the two groups from having surgery to participating in the study might had influenced the results of this study though the authors reported no statistical significant difference on the descriptive variables.

In another RCT study, Cooper et al. (2005), PEDro scale 7/10, compared between a group who performed proprioceptive and balance exercises against a group who performed strengthening training during ACLR rehabilitation. No significant differences between the two groups were found on hop testing at 6 weeks following ACLR surgery. However in most items of Cincinnati scores, strengthening group demonstrated better improvement than proprioceptive group (pain; d = 0.29, swelling; d = 0.26, overall condition; d =0.3, ($p < .05$). The result might indicate that strength programme could offer more benefit in the early phase of ACLR rehabilitation than proprioceptive training. However this study had assessed participants only in the early phase (6 weeks after surgery) of rehabilitation and therefore it is difficult to draw a conclusive statement on the outcomes used.

2.4.3 Intensity of training and patient's compliance

Overall, the mean of the period of intervention for the accelerated protocol of the articles included in this review was 7.25 weeks [ranged between 2 weeks (Shaw et al. 2005) to a maximum of 12 weeks (Beynnon et al. 2011). In addition, the means of number of sessions/week, sets, weight and time were 3, 3, 70% repetition maximum (RM), 30 minutes, respectively, for the accelerated studies included in this review.

Although Beynnon et al. (2005) and Beynnon et al. (2011) had similar study design, outcome measures and frequency of training (3 times per week), there was however no details given on the intensity of training prescribed to the participants. While Beynnon et al. (2005) didn't assess thigh strength and Beynnon et al. (2011) found significant improvement in thigh isokinetic muscle strength at 3-month follow-up in accelerated (19 weeks) compared with non-accelerated group, patient's compliance in the non-accelerated groups of the latter two studies was low (40% and 53% in Beynnon et al. (2005) and Beynnon et al. (2011), respectively. Table 2.5 shows a summary of the means frequency, sets, weight, duration and period of intervention of the accelerated studies included in this review.

Table 2.5: Means frequency, sets, weight, duration and period of intervention of the articles on accelerated rehabilitation within the systematic review.

Number of studies	Mean session/week	Mean sets	Mean weight	Mean duration	Mean period of intervention (weeks)
10	3	3	70% RM	30 minutes	7.25

On the other hand, Risberg et al. (2007) and Risberg and Holm (2009) offered full details on the intensity and frequency of the training intervention (2-3 times per week for 6 months involving strength training of 3 sets (8 to 12 repetitions) at 50% to 80% 1RM, then 3 sets (6 to 8 repetitions) in the final phase of rehabilitation. Risberg et al. (2007) found no difference in the objective measures (single leg hop test, isokinetic muscle strength and proprioception) between the 2 groups while Risberg and Holm (2009) found significantly improved isokinetic hamstring strength for strength training group compared with neuromuscular group. With good compliance to both rehabilitation programmes in the latter studies (NE: 71%, SE: 91% for Risberg et al. (2007) and Risberg and Holm (2009), respectively, the study of Risberg and Holm (2009) offers an indication to the superiority of strength training in the hierarchal order of rehabilitation exercises, and that focus should be predominantly on strength and not neuromuscular training in the acute phase of ACLR rehabilitation. There were two studies in this review which have not reported the compliance of participants to the rehabilitation programmes (Perry et al. 2005, Heijne and Werner 2007).

Apart from these four studies, the remainder of studies demonstrated heterogeneity in the dosage (intensity and frequency) of training as presented in Table 2.2. These variations could have contributed to the non-significant findings of outcomes measures observed in some studies. For instance, while majority of studies introduced early exercise to the intervention group, Perry et al. (2007) started to introduce the OKC for quadriceps by week 8 following ACLR reconstruction as compared to week 5 in Tagesson et al. (2008) and week 4 in Heijne and Werner (2007). It is interesting that with late introduction of OKC, Perry and colleagues found that OKC group had shown no significant difference between treatment groups in knee laxity or leg function. It would have been interesting however to see the results of isokinetic thigh strength had it been tested in the latter study.

In addition, it is interesting to observe that group performing quadriceps exercises in the study of Shaw et al. (2005) had shown significant improvement in knee ROM compared to those who didn't perform, but no significant differences between the two groups were observed for quadriceps lag, functional hop, isokinetic quads and laxity even though both groups had good compliance to their rehabilitation programmes. Achieving full ROM however might have an important clinical implication on determining the successful knee full recovery as suggested by Biggs et al. (2009). In addition, it could be speculated that improvement in isokinetic quadriceps strength was not expected in the study of Shaw et al. (2005) which had an intervention only in the first 2 weeks following ACLR surgery. Zhou (2003) claimed that it is possible for participants with no exercise training experience to demonstrate rapid increase in strength which can be attributed to the neural adaptations as no muscle size change can be observed in the short term (4-20 weeks) training programmes.

2.4.4 Clinical implications

The evidence from the literature regarding ACL rehabilitation lacks the proper details that can enable a practicing clinician to fully implement the programme to the optimal level. There is no consensus within the literature to suggest the exact dosage and duration of accelerated rehabilitation protocols. Most studies on accelerated rehabilitation have not reported full details of exact content of each rehabilitation phase. This has limited the chance of reproducing the studies and the appropriateness of comparisons between studies. For instance Carey et al. (2013) and Silva et al. (2012) had allowed their patients to rejoin full normal and sporting activities after 5 months following ACLR accelerated rehabilitation while Beynnon et al. (2005) and Beynnon et al. (2011) had allowed the full return after 19 weeks (4.3 months), Tagesson et al. (2008) after 16 weeks and Karasel et al. (2010) after 6 months.

This has left many clinicians without sufficient details when seeking to implement an optimal rehabilitation protocol outlined in the literature. For instance, most articles in the available literature tend to focus on providing details on neuromuscular training programme while other primary issues primary issues contributing to excellent outcomes of ACLR rehabilitation such as ROM, strength and stability, are dealt with as secondary outcomes (Biggs et al. 2009). Based on the available evidence from the literature, it is fair to say that there is a consensus however that accelerated rehabilitation is a programme that allows full return to activity between the periods of 4 - 6 months after ACLR surgery (Heijne and Werner 2007).

The 10-20 years' work of Shelbourne and Klotz (2006) revealed that full knee ROM equal to that of the opposite uninjured knee was the main significant factor of patient's long-term satisfaction. This is in agreement to the emphasis given by Shaw et al. (2005) and Biggs et al. (2009) on the importance of achieving full ROM and its role in determining the successful outcomes of ACLR surgery. Based on these studies, it can be speculated that ROM seems to be the top priority for all types of surgery and should be achieved within a particular time frame (as early as day 1 post-operatively; (Shaw et al. 2005, Biggs et al. 2009, De Carlo and McDivitt 2006). In addition, the management of pain and swelling as well as early ambulation are common early phase's goals to all types of ACLR surgery.

However, the reminder of exercises including proprioceptive, weight bearing and strength trainings can be packaged differently depending on individual's tolerance of neuromuscular and psycho-biological states. On the basis of Heijne and Werner (2007) study, it seems that OKC for quadriceps offers superior advantage if introduced earlier in the P4 group after ACLR surgery. However, although H4 group demonstrated lower hamstring strength, introducing early OKC hamstrings exercise to this group of patients caused significantly increased knee laxity even though the significance was considered to be clinically irrelevant. But the latter study concluded such laxity increase might be of significance if a participant is to be involved in sports demanding high lower limb positioning and precision.

In addition, although all studies included in this review have deployed accelerated rehabilitation, some author's definition with respect to accelerated rehabilitation differed. For instance amongst the rejected studies, Vadalà et al.(2007) had an "accelerated rehabilitation group" in which participants in intervention (accelerated) group had to be only brace free compared to the control group while performing the same rehabilitation. Therefore, the term "accelerated" rehabilitation seems to be inappropriate or unnecessary to use especially with the emergence of more evidence based practice and the continuous shift in the rehabilitation as a result of such practice. The time frame of each phase of ACLR rehabilitation should be determined by both clinical experience and individual response to the programme (De Carlo and McDivitt 2006). In addition, progression between different phases of rehabilitation should take into account the individualized decisions, the achievement of goals of each phase and clinical reasoning.

2.4.5 Limitations of the review

Some studies had assessed patient's baseline measures including ROM, swelling and strength measures at different times. For instance, two studies had assessed participants' outcome measures immediately after surgery (Shaw et al. 2005, Cooper et al. 2005) and two studies did not assess these measures at all before the surgery (Tagesson et al. 2008, Perry et al. 2005). Therefore it was difficult to compare the outcomes measured before surgery in some studies with the outcomes measured immediately after surgery in other studies.

Moreover, although several studies have emphasised on the importance of pre-operative rehabilitation in the knee recovery, all the RCTs included in this review, with the exception of one study (Heijne and Werner 2007), have not included pre-operative rehabilitation as part of the complete package of accelerated rehabilitation protocol. Pre-operative rehabilitation has been reported as a contributing factor towards achieving successful rehabilitation outcomes after the ACLR surgery (Shelbourne et al. 2006b, De Carlo and McDivitt 2006). In addition, because muscle-strengthening exercises can be performed in a variety of forms including isometric, isotonic and isokinetic, concentric and eccentric, closed kinetic chain and open kinetic chain, it was difficult to draw a comparison between the studies with each having different forms of strength training exercise and assessed with different parameters including maximal voluntary contraction (MVC), one repetition maximum (1 RM) and or peak forces/torques.

2.5 Conclusion

In summary although some RCT studies have shown no significant difference exist between accelerated and non - accelerated rehabilitation programmes, there is still sufficient evidence within the literature to demonstrate that accelerated rehabilitation following ACLR is an effective programme and offer superior advantage in terms of improvement in knee ROM, neuromuscular and patient self-reported outcome measures which ultimately leads to safe return to daily and sporting activities without causing harm or compromising the integrity and stability of the new ACLR graft. However while such findings seems to be promising, there is still a need for further prospective, blinded, randomized clinical trials in which a comparison can be made between accelerated and contemporary rehabilitation before the former rehabilitation programme can be considered safe and most appropriate. Future research should also focus on quantifying the exercise volume of accelerated conditioning associated with ACLR rehabilitation.

3 Chapter Three: Genetic Influence on Responsiveness to Strength Training

(A Systematic Review of the Literature)

Abstract

Objective

Significant associations between biological markers of different gene polymorphisms and muscular strength have been reported. However, the influence of genotype on an individual's responsiveness to strength training programmes has received relatively little attention in the literature. The aim of this review was to investigate the extent and robustness of evidence for genetic influences on responsiveness to conditioning for muscular strength with its proxy terminologies of 1 repetition maximum (1RM), peak torque and force.

Design/Method

A systematic review was undertaken from February 2013-May 2014. The search strategy of this review included the electronic database search of Medline, CINAHL, and SPORTDiscus using EBSCOHost search engines. The bibliographies associated with the review articles of the electronic data were searched in order to identify further additional relevant articles. The methodological quality of this review was assessed using specific criteria including phenotypic muscular strength with its measurement proxy; 1 RM, peak torque and force. The search keywords included gene*, influence OR effect OR interaction, response to training OR response to exercise OR response to physical activity, and muscular strength OR peak torque OR peak force OR one repetition maximum.

Results/Conclusion

18 studies were included of which 2 were randomised control trials (RCTs), 4 were cohort, 10 were cross sectional and 2 were twin and family studies. Results showed that ACTN3 R577X, ACE Insertion/Deletion, rs 1024610 polymorphism of chemokine (C-C motif) ligand (CCL2) and rs768539 of its receptor (CCR2) and Insulin Growth Factor (IGF1) repeat promoter polymorphisms can be considered significant contributors to rates of adaptation during conditioning for strength. Intra-genotypic responses to conditioning were heterogeneous with relative effect sizes (Cohen's *d)* for strength gains over congruent periods ranging between 0.1- 8.06. Duration, intensity and frequency of strength conditioning were factors that contributed expectedly to the differential responses of genotypes in regulating gains in strength. The latter was most likely determined by interactive effects of several genes rather than by a single gene.

3.1 Introduction

3.1.1 Rationale for review

Heredity is defined as the variation observed in an individual's characteristics that can be accounted for by variation in genes. The environment may affect the degree to which a hereditary trait (phenotype) develops. A large part of genetics seeks to examine which of the many parts of the environment may affect a particular phenotype. Accordingly it is due to heredity and genetic variability that we observe the heterogeneity in human capability for physical performance and its response to such performance (Thomaes et al. 2011, Tiainen et al. 2009). A vast array of human phenotypes (e.g. maximal oxygen uptake [VO2 max] and endurance) play important role for determining our capability for sports and physical performances.

Although it is well known that genes have large effect on phenotypes such as height and hair colour, their relatively small to moderate effects on phenotypes such as fitness level is largely influenced by the environment [for instance fitness level can be improved by regular exercise] (Skinner 200). The complex characteristics of phenotypes are believed to contribute to the major variations observed in individuals to a particular stimulus such as exercise conditioning as well as the ability of individuals to adapt to such a stimulus [i.e. responsiveness to conditioning] (Beunen et al. 2010). Therefore it is very common to find high responders, average responders and low responders to a particular phenotype (e.g. endurance exercise).

This nature versus nurture interaction is widely known as gene-environment interaction in which the following questions come under investigation; how much of the variability observed between different individuals is due to genetic differences, and how much is due to differences in the environments under which the individuals developed (Perusse et al. 2013). However, considerable individual differences in the response of genetic markers to exercise training have raised the level of challenge to research in understanding the complexity of heredity interacting with complex environments. Each one of these phenotypes is a result of complex interaction between the human anatomical, biochemical and physiological systems. Therefore, it is difficult to detect the response to exercise training due to both the heterogeneity and the influence of multiple components in genetic studies. Moreover, several genes rather than one single gene influence the small to moderate effect sizes demonstrated in genetic studies. Lastly genetic effect is primarily context dependent (Giaccaglia et al. 2008, Charbonneau et al. 2008, Pescatello et al. 2006).

The individual differences in response to exercise training were also evident in the study results of Hagberg et al. (1999) in which sedentary men were underwent 9 months of endurance training and were genotyped for the apolipoprotein E (apoE) gene. The latter study findings showed that subjects with an apoE2 allele (one of three variant or allele forms of the apoE gene) demonstrated significantly greater increases in high-density lipoprotein cholesterol than subjects with either apoE3 or apoE4 alleles while the study of (Hagberg et al. 1999) demonstrated that the apoE2 allele had a lesser response in both systolic and diastolic blood pressure after performing the same exercise training. The results of these two studies demonstrated that the same apoE genotype showed both positive and negative interactions to differentially influence physiological responses to exercise training.

The multiple forms of a single gene that can exist in an individual or among a group of individuals, referred to as polymorphism, have been associated with muscular strength and are well documented in several studies (Sood et al. 2012, Thomis et al. 1998, Pescatello et al. 2006, Lima et al. 2011). Research focused on gene-environment interaction has extensively involved investigations of gene polymorphisms that affect quantitative measures (e.g. bone density) that might be influenced by exercise or investigations of disease outcomes that are influenced by both genetic effects and exercise [e.g. high blood pressure in exercising and non-exercising individuals] (Bray 2000). However, Bray (2000) claimed that a limited number of researchers have investigated the genetic basis of exercise or activity level as a phenotype itself.

From a clinical perspective, a better understanding of the role of genes in the regulation of muscular strength and adaptation would be useful for medical staff and scientists working in various fields including rehabilitation and sports performance departments. If identifying the good and poor exercise responders before prescribing an exercise programme was possible, then it seems realistic to design and prescribe exercise or training programmes according to the individuals' response which in turn would facilitate the achievement of an optimal level of performance (Williams et al. 2005). Studies with the hypothesis that the genetic makeup is having a direct effect on the characteristics of physical activity and is potentially influencing the response to such activity are very limited.

3.1.2 Measured and unmeasured approaches

The search for the genetic basis of responsiveness to particular phenotypes including physical training is based on two approaches; the measured and unmeasured approach. The unmeasured approach is normally used when the measured genotype is not available and inferences about the influence of genes on a particular phenotype are based on statistical analyses of the distributions of measures in related individuals and families. Twin and family studies are the main unmeasured approaches in genetics that have provided researchers with a better understanding of the gene-environment interaction (Perusse et al. 2013). Twin and family studies offer researchers an opportunity to differentiate origins of familial resemblance that may potentially arise from shared genes, shared environments, or both (Thomis et al. 2004). For instance in studies where the monozygotic MZ twins (i.e. twins with a 100% share of the same genes) demonstrate greater similarity compared to dizygotic DZ twins (i.e. twins with that share 50% of the same genes) the evidence for the genetic influence on the trait or phenotype is higher (Beunen et al. 2010).

The measured approach attempts to identify genes that explain variability in human phenotypes. The measured approach has two main strategies; Quantitative Trait Loci (QTL) linkage analysis and allelic association studies. The former refers to the localisation of individual “loci” that make up the components of a particular phenotype. A QTL is a region of DNA that is associated with a particular phenotypic trait while the term “linkage analysis” refers to study aimed at establishing linkage between genes inherited together because of their location near one another on the same chromosome (Beunen et al. 2010). Although the QTL linkage analysis may contain genes affecting health status, it also offers the advantage that no knowledge of physiological mechanism influencing distinct characteristics of the phenotypes would be required as collecting such information can be time consuming and expensive (Kendziorski et al. 2002). However, linkage analysis studies require the cooperation of genetically related subjects.

The second strategy is allelic association studies in which a specific marker allele (genotype) is studied within a candidate gene in groups of different genotypes (Rankinen et al. 2006). In comparison to QTL linkage analysis studies, the association studies do not require genetically related subjects (Beunen et al. 2010). The association studies in genetic fields fall into two main categories; case-control and cross sectional studies. The case-control design studies incorporate a comparison, for instance, between genotype frequencies of endurance athletes and a control group whereas cross sectional studies examine, for example, participants with different genotypes on their physical performance phenotypes (Macarthur and North 2005).

Several genotypes have been found to have association with the fitness capability phenotypes (Sood et al. 2012, Thomis et al. 1998, Pescatello et al. 2006, Lima et al. 2011) and in particular in response to muscular strength training. For instance, one of the genetic polymorphisms that have been significantly associated with response to training is ACTN3 R577X. Several studies have particularly shown association between R allele of ACTN3 R577X genotypes and increases in musculoskeletal strength (Clarkson et al. 2005, Norman et al. 2009, Yang et al. 2003). In addition the D allele of ACE I/D polymorphism have also been associated with response to muscle strength training (Muniesa 2010, Lima et al. 2011). Other gene polymorphisms associated with response to strength training are Adrenergic receptor ADR β2Glu27 (Yao et al. 2007), rs 1024610 polymorphism of chemokine (C-C motif) ligand (CCL2) and rs768539 of its receptor [CCR2] (Harmon et al. 2010) and Insulin Growth Factor (IGF1) repeat promoter polymorphisms (Kostek et al. 2005).

Presently the gene-environment interaction between candidate gene polymorphisms and responsiveness to physical conditioning is still largely understudied (Beunen et al. 2010), and to our knowledge there are no previous studies that have considered the genetic influence in rehabilitative populations. Therefore this review seeks to summarise contemporary strategies for evaluating the contribution of gene influence to the capability for functional and physical performance. It also assesses how the interaction between genes and environment (strength training) might affect the variability of physiological adaptation and responsiveness to conditioning stimuli. A better understanding of the interaction of gene polymorphisms in response to different types of exercise will permit clinicians and sports rehabilitation specialists to develop improved training programmes capable of optimizing rehabilitation outcomes (Hawley 2009).

3.2 Methods

3.2.1 Information sources and search strategy

The search strategy of this systematic review adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Electronic database search was undertaken in three main bodies of electronic data search; Medline, CINAHL and SPORTDiscus using EBSCOHost search engine. The following keywords were used and entered into databases under four main themes;

Theme 1; Gene* (with * to include the relevant keywords such as genetics, genes and genotypes).

Theme 2; Influence OR Effect OR Interaction

Theme 3; Response to Training OR Response to Exercise OR Response to Physical Activity.

Theme 4; Muscle Strength OR Peak Torque OR Force OR Repetition Maximum OR RM.

Keywords within each theme were combined together with the word ‘OR’. The results of each theme were then combined using the word ‘AND’ to get the final number of published articles in this systematic review. Table 3.1 shows the overview of the keywords used in this review.

3.2.2 Inclusion and eligibility criteria

The search was limited to articles published in the English language from the year 1998 to year 2013. Review studies were not included in this systematic review. Familial studies, RCTs, cohorts, case control trials and cross sectional studies were included in the study. In addition only healthy participants aged between 18 and 60 years old were included, irrespective of their phenotypic fitness or activity levels. With regards to outcome measures only exercises or physical activity trainings related to strength were considered in this study. The phenotypic measures included in this review were muscular strength including its measurement proxy terms, one repetition maximum (1 RM), peak torque and force.

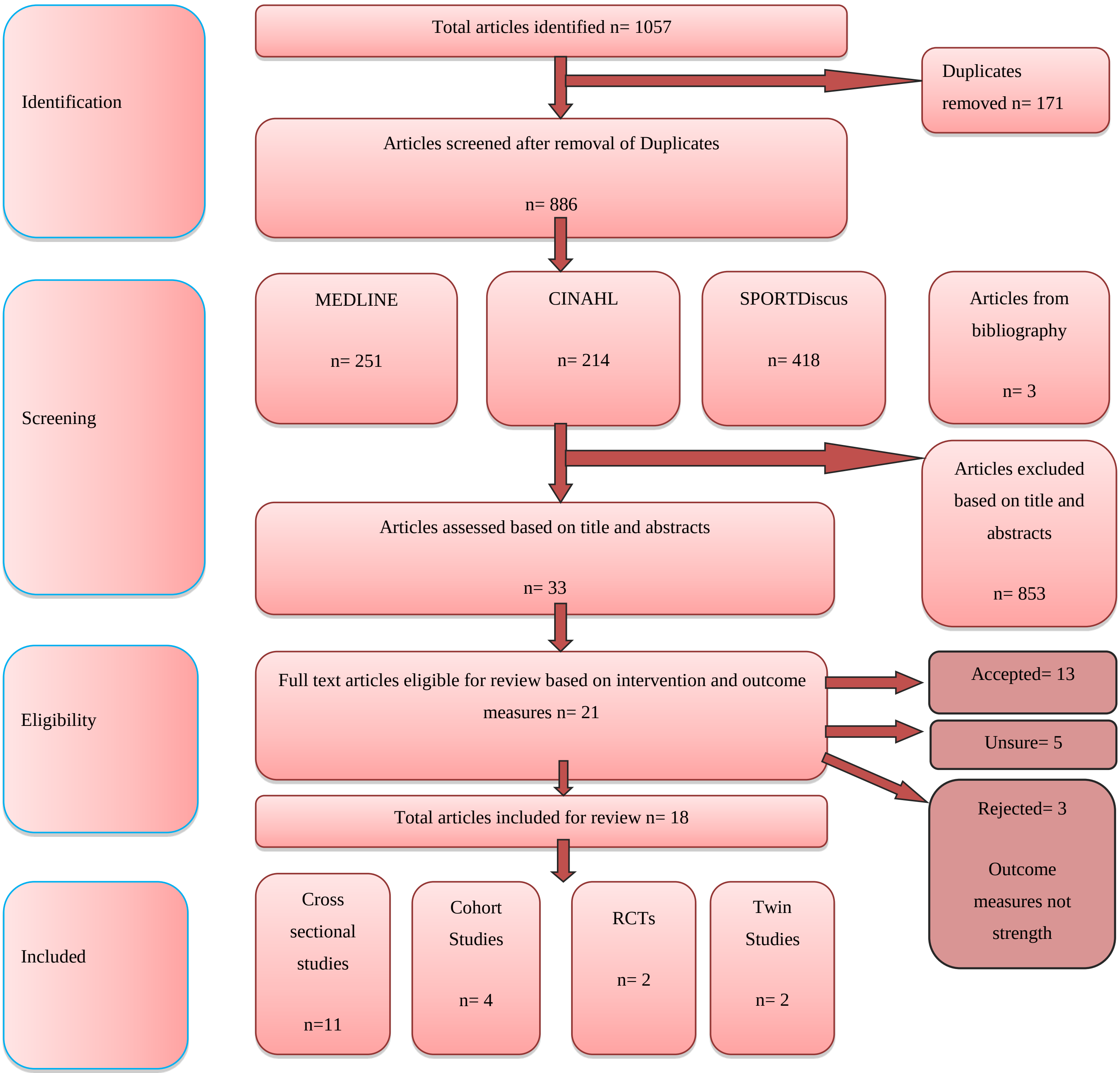
3.2.3 Data extraction

A schematic representation of the study selection process is presented in Figure 3.1. Initially, two independent reviewers performed the literature search. All the relevant titles were selected first from the list obtained from the electronic database searches. Each reviewer examined publications fulfilling the inclusion criteria. The duplicates of these articles were first removed and then the title and abstracts of the remaining studies were scrutinised based on the inclusion and exclusion criteria mentioned above. Some studies were excluded because neither the outcome measures nor the interventions were consistent with the inclusion criteria of this review. The reviewers then divided the studies into three categories; ‘include’, ‘unsure’ or ‘reject’. The full paper of all the abstracts labelled as either ‘unsure’ or ‘include’ were read first. This procedure was followed so as to avoid the rejection of any useful papers and articles. The studies in the “reject” category (n=3) were excluded because the outcome measures were other than muscle strength (1RM, peak torque and force). The reference lists of relevant articles were searched manually in an attempt to identify further additional articles that were not originally identified in the database search. Consensus was used in the final outcome of this systematic review to resolve any disagreements between the two reviewers.

Table 3.1: Overview of the keywords and the combinations used for the review.

	Keywords	Combination	Final Combination
Subjects	Healthy subjects expressing genotypes responsive to training		
Type of Study	1) Gene *		
Condition	2) Influence 3) Effect 4) Interaction	11) 2 OR 3 OR 4	
Intervention	5) Response to Training 6) Response to Exercise 7) Response to Physical Activity	12) 5 OR 6 OR 7	
Outcome measures	8) Muscle strength 9) Peak torque OR force 10) Repetition Maximum (RM).	13) 8 OR 9 OR 10	
Condition AND Intervention AND Outcome measures			1 AND 11 AND 12 AND 13

Figure 3.1: Flow chart illustrating the process used for selecting the relevant studies of this review (based on PRISMA guidelines).



3.3 Results

This paper provides a systematic review of the influence of selected genotypes of gene polymorphisms on the extent of responsiveness to muscular strength conditioning with its proxy terminologies of 1RM, peak torque OR force). Using the EBSCO search engine a total of 1057 studies were retrieved from Medline, CINAHL and SPORTDiscus databases. After the removal of duplicates the remaining 886 studies were scanned of which 214 studies were from CINAHL, 418 were from SPORTDiscus and 251 were from MEDLINE. In addition, the reference lists of these articles were manually scanned to find out any additional relevant articles. As a result, 3 additional and relevant studies were found during this process making it a total of 21 studies for this review. Of the 21 studies selected as relevant articles, 13 were in the ‘included’ category, 5 studies were in the ‘unsure’ category and 3 studies were in the ‘reject’ category. Therefore the final total number of studies eligible for this review has produced 18 studies. Of the 18 studies for this review, 2 were RCTs, 4 were cohorts, 2 were twin and family, and 10 were cross sectional studies. Table 3.2 shows an overview of the studies included in this review and Table 3.3 offers associated descriptions of the effects of strength conditioning interventions.

Table 3.2: Overview of studies included within review.

Article	Type of Study	Pedro Scale	Gene Polymorphism	Subject and Activity Level	Training Exercise	Training Duration	Training Intensity & Frequency	Outcome Measures	Results
Colakoglu et al. (2005)	RCT: 3 groups	6/10	ACE I/D	99 Caucasian non elite males	SSG & MSG underwent strength-training program (9-11 muscle groups) with 12–15 and 8-12 RM mesocycles.	6 weeks	SSG and MSG trained 3 times/week for 6 weeks. 60–70% of 1 RM first 3 weeks, 70–80% of 1 RM last 3 weeks.MSG did 3sets/exercise of same load. SSG did 1 set for each exercise.	1 RM in half squat and bench press (%).	Subjects with DD had significantly more strength gains in both groups (SSG, MSG)
Giaccaglia et al. (2008)	RCT	6/10	ACE I/D	213 Older men and women, overweight & obese	Knee extensor strength, walking distance .Self-reported physical disability score.	18 months	Walking and light weight lifting for one hour 3 times/wk.2 sets of 12 repetitions of: leg extension, leg curl, heel raise, step up.	Concentric knee strength (Nm/kg body weight)	DD genotype showed greater gains in knee extensor strength compared to II.
Gentil et al. (2011)	Cross sectional	N/A	ACTN3 R577X	141 young men	Knee extensor resistance training	11 weeks	2 sets of 8-12 repetitions of 5 exercises (extensors)- 2 days/week	1RM (N) bench press, knee extensors peak torque (N.m)	R577X polymorphism is not associated with baseline muscle strength or with muscle strength

Table 3.2: Overview of studies included within review.

									response to resistance training
Delmonico et al. (2007)	Cross sectional	N/A	ACTN3 R577X	157 healthy, sedentary old men and women	Air-powered resistance knee extension machines	10 weeks	Unilateral knee extensor, 3 times per week for 10 weeks	1 RM (N) & Peak Power PP (W)	In women XX group had relative (70% 1 RM) PP that was higher than in RR (p=002) and RX groups (p=0.08).
Norman et al. (2009)	Cross sectional	N/A	ACTN3 R577X	120 men and women moderate to well-trained	Maximal 30 seconds Wingate cycling (resistance 7.5% subject's mass	Day of test	2 exercise bouts on day of test with 20 min rest	Peak power (W/kg BW), Peak torque (%), fatigability output	Repeated exercise bouts prompted an increase in peak torque in RR genotype
Clarkson et al. (2005)	Cohort	N/A	ACTN3 R577X	247 men and 355 women	Elbow flexor/extensor resistance training (non-dominant arm),	12 weeks	2 times/week (45 minute each).Week1–4: 3 sets * 12 repetitions of 12 RM weight. Week 5–9: 3 sets * 8 repetitions of 8 RM weight. Week	Isometric Elbow flexion (MVC, kg) , dynamic 1 RM, kg	About 2% of baseline MVC and of 1-RM strength gain after training were attributable to ACTN3 XX genotypes

Table 3.2: Overview of studies included within review.

							10–12: 3 sets *6 repetitions of 6 RM weight (non-dominant elbow)		
Lima et al. (2011)	Cross sectional	N/A	ACE I/D & ACTN3 R577X	Old 246 women	Knee extension, hamstrings curl, leg press, hip abduction	24 weeks	3 times per week in 24 weeks. 60 % of 1RM (first 4 weeks), 70 % (next 4 weeks,), 80 % (remaining 16 weeks). Repetitions decreased from 12, 10 and 8.	Dominant knee extensor isokinetic peak torque (MVC). Peak torque (N.m)	In response to RT, II significantly increased FFM and significant training×genotype interaction was found.
Pescatello et al. (2006)	Cohort	N/A	ACE I/D	631 men and women	Elbow flexor/extensor resistance training (non-dominant arm),	12 weeks	2 times/week (45 minute each).Week1–4: 3 sets * 12 repetitions of 12 RM weight. Week 5–9: 3 sets * 8 repetitions of 8 RM weight. Week 10–12: 3 sets *6 repetitions of 6 RM weight (non-dominant elbow)	Isometric Elbow flexion (MVC, kg) , dynamic 1 RM, kg	ID explained 1% of the MVC response to RT in T and 2% of MVC, 2% of 1RM, and 4% of CSA response in UT

Table 3.2: Overview of studies included within review.

Folland et al. (2000)	Cross sectional	N/A	ACE I/D	33 healthy male	Strength training for quadriceps muscles	9 weeks	3 sessions/week for 9 weeks. One leg of each subject performed isometric while the other leg carried out only dynamic training.	Peak torque % (Isometric and isokinetic)	Significant greater strength gains in subjects with the presence of D allele
Williams et al. (2005)	Cross sectional	N/A	ACE I/D	81 untrained men, 44 performed strength program	Quadriceps dynamic muscle strength	8 weeks	10 repetitions (unilateral knee extension) at 100% 10-RM load, 3 times/week for 8 weeks	Isometric, isokinetic strength (MVC at 1.57 rad (N).	ACE had no significant association with 9–14% mean increases of muscle strength in response to the training intervention.
Charbonneau et al. (2008)	Cohort	N/A	ACE I/D	86 inactive men, 139 inactive women	Unilateral knee extensor ST (dominant)	10 weeks	3 times/week (30 minute each), multiple sets of unilateral knee extension exercise designed to individualize loads (near maximal effort)	1RM (kg), muscle volume (MV, cm^3)	No associations observed for 1RM in adaptations to ST in men or women
Sood et al. (2012)	Cross sectional	N/A	IGF1 repeat promoter	114 Old healthy men and women	Unilateral knee extensor ST	10 weeks	3 times/week for 10 weeks. 5 sets (near-maximal effort knee	PP of 1 RM (W)	No significant influence in changes in knee

Table 3.2: Overview of studies included within review.

							extension) for participants <75 years old & 4 sets for participants >75 years old.		extensor PP following ST programme
Hand et al. (2007)	Cross sectional	N/A	Insulin like growth factor (IGF)	128 men and women, physically inactive relatively healthy	Unilateral knee extension ST programme.	10 weeks	3 times/week (30 minute each), multiple sets of unilateral knee extension exercise designed to individualize loads (near maximal effort)	1 RM strength , muscle volume (MV)	2 of the 3 IGF1 repeat promoter influence muscle phenotypic responses to ST
Kostek et al. (2005)	Cross sectional	N/A	Insulin like growth factor (IGF)	67 Caucasian inactive older men & women	Unilateral knee extension ST programme	10 weeks	3 times/week for 10 weeks. 5 sets (near-maximal effort knee extension) for participants <75 years old & 4 sets for participants >75 years	1RM (N), muscle volume (MV, cm^3)	192 allele carriers gained significantly more strength with ST than non-carriers

Table 3.2: Overview of studies included within review.

							old.		
Yao et al. (2007)	Cross sectional	N/A	Adrenergic receptor (ADR) β2Glu27	98 Healthy middle-aged and older men and women	Unilateral ST for Knee extensor	10 weeks	3 times/week for 10 weeks. 5 sets (near-maximal effort knee extension) for participants <75 years old & 4 sets for participants >75 years old.	1RM (N), muscle volume (MV, cm^3)	Substantial increase in 1 RM in those carrying ADRβ2 Glu27
Harmon et al. (2010)	Cohort	N/A	CCL2 and CCR2	874 college aged subjects	Supervised ST of elbow flexion	12 week	2 times/week (45 minute each).Week1–4: 3 sets * 12 repetitions of 12 RM weight. Week 5–9: 3 sets * 8 repetitions of 8 RM weight. Week 10–12: 3 sets *6 repetitions of 6 RM weight (non-dominant elbow)	Dynamic 1 RM (kg), Isometric elbow flexion (peak torque N.m).	CCL2 & CCR2 had strong associations with increased strength in response to strength program

Table 3.2: Overview of studies included within review.

Thomis et al. (1998)	Twin study	N/A	N/A	Monozygotics MD= 25 and Dizygotic, DZ=16 Male	Resistance training for the elbow flexors	10 weeks	5 sets biceps curl, 3 times/week. Every week the load of each set (0.5 kg) [percentage of 1 RM]	1RM (kg), Isometric, concentric and eccentric moments (N.m)	20% of the variation in post-training 1 RM, isometric, concentric moment was explained [genetic factors]
Thomis et al. (2004)	Twin study	N/A	ACE I/D	57 males: 16 pairs DZ, 25 pairs MZ male	Resistive elbow flexor training	10 weeks	5 sets of biceps curls, 3 times/week. Set 1, 14 repetitions (60% 1RM), set 2, 12 reps (75% 1RM), set 3, 10 reps (80% 1RM), set 4, 8 reps (85% 1RM) and set 5, (70% 1RM) to failure.	1 RM (kg), Isometric, concentric elbow flexor torque (N.m)	Responses to the strength train were not associated with I/D genotype.

Table 3.2: Overview of studies included within review.

SUMMARY AND KEY:	
N/A: Not Applicable.	Pedro Scale:
CG: Control group	1) Eligibility criteria were specified.
SSG:Singl set group.	2) Subjects were randomly allocated to groups.
MSG:Multiple set group.	3) Allocation was concealed.
MVC: Maxiaml Voluntary Contraction	4) The groups were similar at baseline.
DZ: Dizygotic.	5) There was blinding of all subjects.
MZ: Monozygote.	6) There was blinding of all therapists.
FFM:Fat-free mass.	7) There was blinding of all assessors.
BW: Body weight.	8) Measures of at least one key outcome were obtained from more than 85%of the subjects.
RT: Resistive training.	9) Subjects for whom outcome measures were available received the treatment or control condition.
PP: Peak power.	10) Results of between-group statistical comparisons are reported.
	11) The study provides both point measures and measures of variability.

Table 3.3: Genotypes and their relative effect sizes (Cohen d, pre and post strength training intervention) of studies included within review.

Studies	Gene polymorphism	Outcome measures	Genotype	pre mean$_1$	sd$_1$	post mean$_2$	sd$_2$	Raw ES	Cohen *d*
Colakoglu et al. 2005	ACE I/D	SSG Squat 1RM (kg)							
			DD	119	10	153	12	3.10	
			ID	113	11	143	12	2.56	0.83 [a]
			II	107	11	132	14	1.98	1.6 [a]
Giaccaglia et al. 2008	ACE I/D	Knee extension (Nm.kg BW)							
			II	2.89	0.8	2.72	0.68	-0.01	0.24 [c]
			ID	2.82	0.61	3.00	0.68	0.01	0.15 [c]
			DD	2.32	1.05	2.87	0.42	0.03	
Gentil et al. 2011	ACTN3 R577X	Knee extension peak torque (N.m)	XX	224	39	240	39	0.41	0.075 [d]
			RX	223	35	238	37	0.42	0.12 [d]
			RR	229	43	243	42	0.33	
Delmonico et al. 2007	ACTN3R577X	1RM (N) knee extension (men)							
			XX	307	88	388	98	0.87	0.87

Table 3.3: Genotypes and their relative effect sizes (Cohen d, pre and post strength training intervention) of studies included within review.

		1RM (N) knee extension (women)	XX	159	92	205	54	0.61	0.61
Norman et al. 2009	ACTN3R577X	Knee extension peak torque % (at all angular velocities)	RR	% Increase after second bout 4-10 %					
			XX	% Increase after second bout 0.5-2 %					
Clarkson et al. 2005	ACTN3R577X	Women elbow flexion MVC (kg)	XX	62	41	74	66	0.22	
			RX	70	34	83	53	0.29	0.15 [e]
			RR	68	39	82	61	0.27	0.126 [e]
Lima et al. 2011	ACE I/D	Knee extension peak torque (N.m)	DD	92.60	3.80	106.7	3.80	3.71	0.26 [h]
			ID	87	3.00	99.2	3.00	4.07	2.28 [h]
			II	99.2	3.80	107.1	3.80	2.08	
Pescatello et al. 2006	ACE I/D	MVC (kg) untrained elbow flexion	II	43	30	45	30	0.08	0.35 [m]

Table 3.3: Genotypes and their relative effect sizes (Cohen d, pre and post strength training intervention) of studies included within review.

			ID	48	25	57	38	0.06	0.07
			DD	47	30	54	45	0.27	
Folland et al. 2000	ACE I/D	Isometric quads MVC (% increase)		II % increase			9		
				ID % increase			18		
				DD % increase			15		
Williams et al. 2005	ACE I/D	Isokinetic quadriceps MVC (N) at 1.57 rad		701	161	787	184	0.24	0.54
Charbonneau et al. 2008	ACE I/D	Knee extension 1RM (kg)	ID	28.4	18.0	32.5	19.5	0.22	0.08 [r]
			DD	31.2	16.5	34.1	18.0	0.17	
			II	32	24.0	33.1	25.5	0.04	0.04 [r]
Sood et al. 2012	IGF1 192 Homozygotes	1 RM 70 % (W) knee extension		296	156	305	256	0.04	0.18

Table 3.3: Genotypes and their relative effect sizes (Cohen d, pre and post strength training intervention) of studies included within review.

	IGF 192 Heterozygotes			326	128	349	213	0.13	0.18
Hand et al. 2007	IGF1	1 RM (kg) knee extension (men)		33	1.0	41	1.2	7.24	8.06
		1 RM (kg) knee extension (women)		22	1.0	27	1.2	4.53	5.03
Kostek et al, 2005	IGF1	IGF1 homozygotes 1 RM (N) knee extension		231	65	298	98	0.81	0.81
		IGF1 heterozygotes		222	65	289	65	1.03	1.03
Yao et al. 2007	Adrenergic receptor ADR	1 RM (kg) knee extension (men)		32	12	42	16	0.64	
		1RM (kg) knee extension (women)		19	10	24	10	0.53	
Harmon et al. 2010	CCR2 rs3918358	% increase in 1 RM elbow flexion	0.7 - 2.5 %						

Table 3.3: Genotypes and their relative effect sizes (Cohen d, pre and post strength training intervention) of studies included within review.

Thomis et al. 1998	Twin study	1 RM (kg) elbow flexion	23	6	35	6	2.16	2.05 [v]
		Isometric elbow flexion (N.m) at 110	52	12	60	14	0.61	0.62
Thomis et al. 2004	ACE I/D (Twin study)	1 RM (kg) elbow flexion	23	6	34	5	2.13	2 [v]
		Isometric elbow flexion at 110 (N.m)	50	10	55	15	0.38	0.39 [v]
							Total *d*	30.07
							Mean *d*	1.01

Table 3.3: Genotypes and their relative effect sizes (Cohen d, pre and post strength training intervention) of studies included within review.

<u>Summary and Keys:</u>

SSG: Single Set Group
MVC: Maximal Voluntary Contraction.
sd: standard deviation

Cohen *d* is calculated as post mean1- post mean2/pooled SD

a: denotes *d* relative to most responsive genotype in the study (DD)

c: denotes *d* relative to most responsive genotype in the study (DD)

d: denotes *d* relative to most responsive genotype in the study (RR)

e: denotes *d* relative to most responsive genotype in the study (XX)

h:denotes *d* relative to most responsive genotype in the study (II)

m: denotes *d* relative to most responsive genotype in the study (ID)

r: denotes *d* relative to most responsive genotype in the study (DD)

x: denotes studies offering group mean comparison between men and women

v: denotes group mean comparison before and after exercise in the unmeasured approach

3.4 Discussion

The evidential approach to gaining information about sports-related genes has to date, been flawed (Hagberg et al. 2011). This fact is also consistent with the study of Harmon et al. (2010) who claimed that the polymorphisms within specific gene loci that could potentially explain the genetic differences between responders and non-responders to strength training programmes have not been clearly identified in the literature.

3.4.1 Type of studies

Several large-scale studies were designed to investigate the effects of genetics on responsiveness to strength training. HERITAGE (Skinner 2001) and Studies of a Targeted Risk Reduction Intervention through Defined Exercise; STRRIDE (Kraus et al. 2001) are two main studies that have examined the effect of genetic factors on the physiological responses to exercise. However, the focus of these two studies was mainly on assessing the response towards aerobic training rather than strength training (Thompson et al. 2004).

Of the 18 relevant studies included for this review, 2 studies (Colakoglu et al. 2005, Giaccaglia et al. 2008) were RCTs, and 3 (Harmon et al. 2010, Pescatello et al. 2006, Clarkson et al. 2005) were part of an ongoing large-scale cohort study named FAMuSS (Functional Polymorphism Associated with Human Muscle Size and Strength). The aim of FAMuSS was to investigate the effect of genetic factors on the physiologic response to resistance exercise training, including muscular strength training. In particular, the study focused on examining the interaction of genetic factors and the change in muscle size and strength with resistance exercise training of the non-dominant arm. The selection of arm training was based on the fact that arms are used less in modern life compared to the legs even among physically inactive individuals. As such the study of the arms may reduce the baseline differences in muscular strength produced by legs that are daily involved in physical activities such as walking (Thompson et al. 2004). In addition, the FAMuSS study excluded any subject who had performed strength training or any physical work requiring repetitive use of the arms 12 months prior to conducting the study in order to reduce baseline differences in muscular strength that might be produced by such routine arm activities at work. Another important ongoing large-scale relevant study of genetic influence on responsiveness to training is the TIGER (Training Interventions and Genetics of Exercise Response) study. The aim of TIGER is to identify the potential genetic factors that may play a role in influencing responsiveness to physical training on college-age individuals who have to follow a programme that consists of performing regular strength training 3 days per week (Sailors et al. 2010). The majority of the remaining studies included in this review (n=11) were association studies in the form of cohort and cross sectional design studies. The remaining two studies of the 18 were twin and family studies (Thomis et al. 1998, Thomis et al. 2004). Although some studies in the review suggested positive effects of gene polymorphisms on responsiveness to strength training, there were some concerns on the methodological quality of the studies reviewed. For instance, the studies of Williams et al. (2005), Kostek et al. (2005), Yao et al. (2007), Norman et al. (2009), Folland et al. (2000) had small sample size hence it would be hard to draw robust and conclusive results from them.

3.4.2 Genotypes responsive to strength training and their relative effect sizes

This review has identified candidate gene polymorphisms that are associated with the gene-environment interaction and their adaptation to strength training. These are ACTN3 R577X (Clarkson et al. 2005, Delmonico et al. 2007, Norman et al. 2009, Lima et al. 2011, Gentil et al. 2011), ACE I/D (Williams et al. 2005, Colakoglu et al. 2005, Pescatello et al. 2006, Folland et al. 2000, Giaccaglia et al. 2008, Lima et al. 2011, Charbonneau et al. 2008), and Insulin Growth Factor (IGF1) repeat promoter polymorphism (Kostek et al. 2005, Hand et al. 2007, Sood et al. 2012), Adrenergic receptor ADR β2Glu27 polymorphism (Yao et al. 2007) and rs 1024610 polymorphism of chemokine (C-C motif) ligand (CCL2) and rs768539 of its receptor (CCR2).

The review has determined the magnitude of the differences between the groups and experimental conditions of some of the relevant studies. Cohen's *d* effect size was calculated using pooled standard deviations for each study that provided absolute mean data and standard deviations. A value of less than 0.4 represented a small magnitude of change (effect size) while 0.41-0.7 and greater than 0.7 represented moderate and large effect sizes respectively.

The results of this review suggested that the responsiveness to strength training associated with the RR genotype of the ACTN3 R577X polymorphisms exceeded that of the RX and XX gentoypes. However, the relative additional gains in strength were 2% and 2% (Clarkson et al. 2005), and 4% and 4% (Gentil et al. 2011), respectively for training durations of the knee extensor musculature lasting 8 and 11 weeks [3 sessions•week-1; 60-70% MVC], with correspondingly small relative effect sizes (0.08 – 0.13; Cohen's *d*, Table 3.3). These findings are consistent with the study of Norman et al. (2009) who had shown that repeated exercise bouts prompted an increase in peak torque in RR carriers but not in XX carriers of the ACTN3 R577X polymorphism. In addition a study by Delmonico et al. (2007) has shown that the homozygous R allele had a significantly greater peak power response to strength training than the homozygous X. However it was not possible to calculate the effect sizes of ACTN3 R577X genotypes in these latter two studies as absolute mean data, standard deviations or standard errors for muscular strength outcomes were not available.

The heterogeneity and differential responses (0.1-8.06; Table 3.3) for gains in strength associated with the same genotype amongst different studies could be due to variations in exercise dosage and in the assessment parameters used. For instance even though there were seven studies in which the same strength outcome (knee extension) was assessed (Kostek et al. 2005, Hand et al. 2007, Yao et al. 2007, Sood et al. 2012, Charbonneau et al. 2008, Lima et al. 2011, Giaccaglia et al. 2008), there was variation in the durations and intensity of the strength training conditioning prescribed for each individual study. The most intensive and prolonged period of dosage was offered by Giaccaglia et al.(2008) and this essentially provided a three-fold increase in exercise stress compared to the least robust conditioning intervention (Williams et al. 2005).

The DD genotype of the ACE I/D polymorphism demonstrated greater strength gains in elbow flexor conditioning compared to ID and II genotypes (range: 14.3% to 38 %; d = 0.07 to 2.00; Colakoglu et al. 2005, Pescatello et al. 2006, Charbonneau et al. 2008; Table 3.3) suggesting that the D homozygote is an important determinant of strength responses to conditioning. Equivalent evidence from two familial and twin studies (Thomis e al. 1998; Thomis et al. 2004) was elusive. In contrast, other studies challenge this evidence and report that individuals possessing the II genotype had greater strength gains compared to those with either DD or ID during 24 weeks of knee extensor conditioning (2% and 56%, respectively; Lima et al. 2011) and statistical trends towards this latter finding associated with 11 weeks of conditioning of the knee extensors (Folland et al. 2000). It is interesting to note that during 11 weeks of elbow flexor conditioning, the ID genotype had been associated with similar responses to the DD genotype but increased responsiveness to conditioning compared to the II genotype [3%] (Pescatello et al. 2006).

In addition, Hand et al. (2007) had compared between different polymorphisms of the IGF1 gene and found there was a significant combined gene effect (IGF1 CA repeat and PPP3R1 I/D) gene polymorphisms on change in strength with strength training ($P < 0.01$). The study of Hand et al. (2007) had also found that individuals homozygous for PPP3R1 II were also heterozygous for the 192 allele for IGF1 and had significantly greater increases in strength with strength training than those homozygous for PPP3R1 II, who were also non-carriers of the 192 allele for IGF1 (8.4 ± 0.7 vs. 4.7 ± 0.9 kg; $P < 0.01$). Moreover, Kostek et al. (2005) showed that the 192 allele of the IGF1 gene promoter had greater quadriceps-muscle strength gains compared with non-carriers ($P = 0.02$), with no differences observed for the muscle-quality response to training.

It is plausible that the observed significant heterogeneity amongst the relative effect sizes (0.01-8.0) for responsiveness to strength conditioning amongst genes and their associated alleles (Table 3.3) might be driven in part by the potential for interactions between them and inherent heterogeneity amongst the responses of the various and small experimental populations comprising the evidence in the literature. This speculation would be supported by evidence from recent association studies in which increasing numbers of genotypes have been linked to optimum genetic combinations facilitating perfection in sporting genotypes in the formation of the perfect combination for perfect sporting genotypes (Puthucheary et al. 2011).

A recent study by Buxens et al. (2011) concluded that 21.4 % of genetic factors account for sports performance. However the question of "which specific genetic profile was responsible for most of athletic performance?" has not been answered yet in many studies. This question therefore become the main focus of recent studies and prompted many researchers to examine the effects of single candidate genes on physical performance. With the fact that the physical activity status phenotype is a complex trait, Eynon et al. (2011) claimed that the effect of a single gene variant in this context is small. This finding was also supported by Hand et al. (2007) who found a significant combined IGF1 CA repeat main effect and IGF1 CA repeat * PPP3R1 insertion-deletion (I/D) gene * gene interaction effect, on the changes in strength following a 10 week unilateral knee extension strength training programme. Moreover, of 11 genetic variants in CCL2 and 5 genetic variants in CCR2, Harmon et al. (2010) found that eight genetic variants have shown strong association with response to strength training. Lima et al. (2011) however examined both ACTN3 and ACE gene polymorphisms and concluded that the results of their study do not support the role of ACE I/D and ACTN3 R577X gene polymorphisms in determining muscle strength in response to strength training programme in older women. The contribution of each gene variant therefore in explaining the variance of complex phenotypic traits is still unknown.

3.4.3 Training intensity and phenotypic measures

As part of a large cohort study, 3 studies in this review (Harmon et al. 2010, Pescatello et al. 2006, Clarkson et al. 2005; Table 3.2, had a similar study design in terms of training exercise (elbow flexors strength training), duration (12 weeks), intensity and frequency of strength training. Although all three studies demonstrated strong associations with increased strength in response to strength programme, comparisons between them was not possible as each study examined different gene polymorphisms (rs 1024610 polymorphism of chemokine (C-C motif) ligand (CCL2) and rs768539 of its receptor (CCR2), ACE I/D and ACTN3 R577X).

However 4 studies examined the promoter region variants of the Insulin-like growth factor (IGF) polymorphism on strength training (unilateral knee extension) response of muscle phenotypes of similar population groups (age range 50 to 85 years old). The training programme consisted of performing knee extension strength training 3 times per week for 10 weeks (5 sets [near-maximal effort knee extension] for participants <75 years old and 4 sets for participants >75 years old). Two studies (Charbonneau et al. 2008, Sood et al. 2012) reported no associations for 1RM (kg) in adaptations to strength training in either men or women and no significant influence in changes in knee extensor peak power following the strength training programme respectively. Hand et al. (2007) on the other hand reported significant combined IGF1 CA repeat main effect and IGF1 CA repeat PPP3R1 insertion-deletion (I/D) gene x gene interaction effect, on the changes in strength following the 10 week programme. This supports the earlier suggestion in this review that genetic influence tends to be polygenic. Lastly, Kostek et al. (2005) concluded that 192 allele carriers of IGF gained significantly more strength with strength training than noncarriers. The differential responses observed in these similarly designed studies suggest that response to strength training in IGF pathway genes is not genotype dependent.

During the assessment of upper body strength, it is widely accepted that the variability within the population is higher than the improvements to be expected after a physical training intervention (Costa et al. 2012). It is therefore fair to say that the studies of Harmon et al.(2010), Pescatello et al. (2006), and Clarkson et al. (2005), part of an on-going large-scale study (FAMuSS), should be treated with caution as this cohort study was based on assessing the forearm strength (elbow flexors) with increased variability in baselines measures. With regards to phenotypic measures, the focus of many previous studies, which were excluded from this review, was not on muscular strength but rather on phenotypes such as VO2 max, endurance and cholesterol levels. It was argued that clinicians in particular should treat the results of measured and unmeasured approaches of genetic studies with caution due to the presence of other potentially contributing and complex factors involved in human exercise physiology such as, VO2 max, and body fat.

Therefore it could be speculated that TIGER studies are very promising studies for several reasons. Firstly they focus on strength phenotype with emphasis on exposing young adults to regular exercise under the supervision of well-trained instructors. Secondly, few exercise intervention studies have targeted this age group and none have provided an exercise intervention for obtaining college credit. Thirdly, because time is often given as a limiting factor in several studies related to exercise adherence, TIGER was designed in such a way that exercise would be included as part of the normal college routine. Therefore future research should focus on using robust experimental designs similar to the TIGER study.

In addition, although the sample size required to have sufficient power will be relatively lower in a well-controlled standardized program compared to that of an exercise programme that is managed by the participants at their home, the studies published to date in exercise genetics and the adaptations to exercise programme are underpowered indicating the importance of recruiting much larger sample sizes.

This review has chosen to investigate the responsiveness of candidate genotypes on phenotypes including muscle strength with its proxy terminologies of 1RM, peak torque and force. Nevertheless these phenotypic measures were evaluated using different tests across the studies. For instance, knee extension and quadriceps strength were the commonest phenotypic tests for many studies (Norman et al. 2009, Yao et al. 2007, Kostek et al. 2005, Delmonico et al. 2007, Folland et al. 2000, Williams et al. 2005, Giaccaglia et al. 2008, Lima et al. 2011, Charbonneau et al. 2008, Gentil et al. 2011, Hand et al. 2007) while for other studies elbow flexion (Clarkson et al. 2005, Harmon et al. 2010, Pescatello et al. 2006, Thomis et al. 1998, Thomis et al. 2004) and half squat and bench press (Colakoglu et al. 2005) strength performance were used instead.

3.4.4 Limitations of the review

It was notable that the majority of the studies in this review (Yao et al. 2007, Kostek et al. 2005, Giaccaglia et al. 2008, Charbonneau et al. 2008, Lima et al. 2011, Delmonico et al. 2007, Hand et al. 2007, Sood et al. 2012) had recruited old age groups (between 50 and 85 years old) making it difficult to generalise these findings to other age groups including young age groups. As such future research should focus on recruiting a younger and more active age group population who might demonstrate higher physiological responses to exercise programmes such as strength training than older age groups.

When investigating the gene-environment interaction, the unmeasured and measured approaches have some limitations due a number of reasons. The main reasons are; the difficulty of detecting the response to exercise training due to the influence of multiple components, the influence of several genes rather than one single gene and the fact that the genetic effect is context dependent (Giaccaglia et al. 2008, Charbonneau et al. 2008, Pescatello et al. 2006). For instance when investigating the genetic predisposition of muscle hypertrophy one has to consider that the exercise prescribed for such purpose has to be linked with training designed for resistance mode only. Many association studies of candidate gene polymorphisms for exercise programmes have been carried out often with conflicting results partly due to the context dependency of the genetic effects (Heck et al. 2004). In addition, given the fact that the effect size of candidate genotypes on exercise-related traits is generally thought to be small, the sample size required to achieve robust statistical significance to reliably achieve or capture such effect sizes will be large (Rankinen et al. 2006).

3.4.5 Implications for clinical practice

Health care providers including physiotherapists could potentially benefit from the assessment of gene polymorphism and performance capabilities in patients that might facilitate the advocacy of better, more effective, efficient and individualised rehabilitative programmes. It could be speculated that this approach might facilitate the use of more aggressive rehabilitative programmes such as those involving an increased dosage of strength conditioning, for those patients able genetically to respond and recover most effectively within differentiated pathways of care. However, it is not yet known whether for instance, an accelerated rehabilitation conditioning designed for patients possessing genotypes that are responsive to strength training offers improved outcomes compared to current contemporary practice. If accelerated rather than contemporary standardised programme of physical conditioning offers superior and more rapid outcomes, consideration should be given to offering such rehabilitation routinely to patients with genotypes (responsive to strength training) in order to enhance clinical care as well as to reduce the economic burden on health systems.

3.5 Conclusion

There is a growing body of research supporting the notion that the response to exercise training may be influenced by genetic variation. However, it is still widely accepted that the effect of gene-environment interactions in the responsiveness of individuals to strength training protocols is largely understudied in the literature (Beunen et al. 2010). The aim of this review was to investigate the extent and robustness of evidence for genotypic influences on responsiveness to muscular strength conditioning. This review demonstrates significant associations between candidate gene polymorphisms and responsiveness to strength phenotypes. The results showed that gene polymorphisms of the ACTN3, ACE, CCL2 and CCR2, and IGF1 are responsive to strength training.

However the genotypes associated with these gene polymorphisms demonstrated inconsistency in the level of responsiveness to muscular strength conditioning with each genotype showing a high response in one study a lower response in another. With the view that at least 20% of the muscle training response is accounted for by genetic factors independent of those exerting pre-training influence (Thomis et al. 1998), the findings of this review do not exclude that ACTN3 R577X, ACE I/D, CCL2 and CCR2 and IGF1 genotypes may modulate responsiveness to strength training but consequently induce differential responses to strength training. In addition, future studies should focus on giving more details on the intensities (dosage) of the strength training programmes to uncover the true effect of genotypes on responses. Although the differential response between genotypes could be due to the different strength training protocols and the different assessments used in the studies, future studies must involve significantly larger sample size to ensure sufficient power in the investigation of what appear to be subtle differences between the genotypes across different gene polymorphisms. Moreover, the evidence associated with this review, the effect of strength conditioning on the rate of adaptation appears to be predominantly polygenic. Future studies might usefully focus on examining more than one gene polymorphism in order to understand the true response of individuals to strength training.

Although the effect of candidate gene polymorphisms on physical activity and exercise has received considerable scientific scrutiny, this review continues to highlight the long-standing challenges to fully understanding mechanisms of interaction with genetic variation and regulation of responsiveness to exercise conditioning. The novelty of this review is that it has focused on the most recent evidence involving gene polymorphism and responsiveness to strength conditioning and the latter’s central role within physical function for clinical and asymptomatic populations.

4 Chapter Four (Study One)

Effect of Accelerated Conditioning on the Outcomes of Knee Rehabilitation Following Anterior Cruciate Ligament Reconstruction

4.1 Introduction

The ACLR population in this chapter is worthy of investigation as injury to ACL is very common amongst people participating in sporting and vigorous physical activities especially given the injury rate of approximately 4 per 1000 athletes in developed countries (Van Grinsven et al. 2010). In the UK the increasing cost of knee ACL reconstruction (ACLR) surgery and the subsequent rehabilitation causes a correspondingly increased economic burden to the National Health Service (NHS). With the advancement of surgical techniques and consequently better surgical outcomes, rehabilitation is currently considered as the determinant variable for successful outcomes following ACLR surgery (De Carlo and McDivitt 2006). In addition, the ever increasing pressure on sports' coaching staff to bring elite athletes as early as possible to back full sporting activity has prompted researchers as well as clinicians to focus their attentions on designing a programme that advocates an early return to the pre-surgery status (Karasel et al. 2010, Melegati et al. 2003). As such, the notion of an accelerated rehabilitation programme was introduced in 1990 by Shelbourne with the aim of guiding patients towards an earlier return to normal functional activity following ACLR surgery (De Carlo et al. 1997).

As mentioned in the systematic review on accelerated rehabilitation in chapter two, accelerated rehabilitation is defined as a programme that offers a structured physical conditioning protocol similar to the current standardised program (6-9 months period) but in which exercises causing significant strain to ACLR could be introduced earlier including early unrestricted weight-bearing, range of motion and early use of quadriceps dominated exercises [4-6 months period after ACLR surgery] (Van Grinsven et al. 2010, Shaw 2002, Beynnon et al. 2005, Silva et al. 2012, De Carlo et al. 1997). Accelerated regimes might have been expected to reduce the cost of healthcare systems compared to other traditional regimes and this would be especially helpful in the current adverse economic climate (Larsen et al. 2009). However, the accelerated rehabilitation regime had been initially engulfed with suspicion and controversy as uncertainty existed on whether or not such programmes might offer compromised stability and integrity of the knee joint. The related uncertainty and fears were mainly that the intensity of conditioning early in the programme might surpass the psycho-physiological and neuromuscular capabilities of the patients and lead to secondary problems including the compromised healing of the ACL that ultimately prolong reliance on the health service-provider (Risberg et al. 2004, Louw et al. 2008).

However, based on the systematic review of accelerated rehabilitation in chapter two, it was apparent that there is no consensus on the "operational" definition of accelerated rehabilitation in terms of the amount of frequency, intensity and time (also known as "FIT") of exercise stress as well as the packaging and hierarchal order of exercises throughout the phases of the ACLR rehabilitation programme. De Carlo and McDivittt (2006) had supported this view and concluded that specific parameters had not been identified to determine the exercise intensity or duration that might potentially lead to successful outcomes of ACLR rehabilitation. The possible explanations for this was highlighted in the Cochrane Collaboration Review by Trees et al. (2009) who had observed great variations in methodological study scores, nature of participants, assessor blinding, outcome measures and time points reported in the studies of ACLR rehabilitation. With such variations, Trees and colleagues concluded that pooling of most of the data was therefore not valid and could not provide sufficient evidence to support one exercise intervention against another during the rehabilitation programme. The summation and recommendation of this review was that randomised controlled trial studies with appropriate outcome measures and surveillance periods using standardized reporting were required.

As accelerated rehabilitation following ACL reconstruction takes a minimum of 4 months (De Carlo et al. 1997, Beynnon et al. 2011), therapists are currently prescribing the sequencing of exercise blindly and without robust evidence of clinical efficacy from the literature. Additionally, achieving rehabilitation milestones earlier have meant that a better assessment of the components and phases of the ACL rehabilitation programme is of paramount importance to examine the risk underpinning the accelerated rehabilitation (Shaw 2002). Based on the available evidence, it is apparent that there is a gap in the literature on robust randomised control trials using validated outcome measures over a significant time scale and on “when and how much” the accelerated rehabilitation programme is required throughout its phases in order to achieve optimal and successful rehabilitation. Therefore it is vitally important to investigate the clinical efficacy and effectiveness associated with the accelerated rehabilitation and its components by selecting outcomes measures that could both determine improvements in the functionality of patients associated with successful rehabilitation following ACLR surgery but also the mechanisms by which gains might occur. It is therefore important however to first identify whether or not the outcomes of successful rehabilitation are clinically meaningful for patients. Therefore the methods section of this chapter will underline and critically evaluate briefly the clinimetric relevance (that is the quality of measurements that are used in health care practice and research) of outcomes of function and neuromuscular performance in patients undergoing ACLR surgery and rehabilitation.

4.1.1 Outcomes of function and neuromuscular performance of knee joint

Physiotherapists use outcome measures essentially to assess, evaluate and justify good clinical practice. There is strong evidence in the literature to suggest that there are deficits in the performance of knee following ACLR reconstructive surgery. These deficits include neuromuscular control, sensorimotor, functional and psycho-biological performances (Karasel et al. 2010, Cates and Cavanaugh 2009). Moreover, there is no consensus over the measures used to determine the readiness of physically active patients for a safe return to normal physical activities (Myer et al. 2006). For example, a study by Ardern et al. (2011) demonstrated that athletes had not been able to return to full competitive sporting activities following 12 months of ACLR rehabilitation. Therefore, any outcome measure that can accurately determine patient's physical and psycho-physiological status and subsequently evaluate patient's readiness to return to both daily activities as well as competitive sporting activities following ACLR rehabilitation would be of high benefit and merit. The three main categories of outcome measures deployed during ACLR rehabilitation are functional, objectives neuromuscular and subjective patient-reported outcome measures (Clark 2001, Karasel et al. 2010). Disassociation among objective and subjective measures of capability related to functional performance could be hypothesised to incite sub-optimal conditioning within rehabilitation therapy with the mismatching of perception and objectivity resulting in the underestimation or overestimation by patients of sense of endeavour and the amount of exercise with compromised results (Hewett et al. 2006). With respect to subjective measures, a study by Kocher et al. (2004) found that it was largely due to the combination of subjective assessments (both symptomatic and functional) that determined patient satisfaction after ACLR surgery and rehabilitation. In addition, the assessment of patient commitment, depression, overall mood, and self-efficacy are vital in shaping and tailoring physiotherapy rehabilitation programme that will appropriately suit the individual physical tolerance as well as mental readiness in the early and advanced stages of ACLR rehabilitation and full recovery (Clark 2001). Some of the most commonly used questionnaires for knee symptoms and function include Lysholm Knee Rating System (Briggs et al. 2009, Brand and Nyland 2009), the International Knee Documentation Committee Subjective Knee Evaluation Form [IKDC] (Grindem et al. 2011, Gleeson et al. 2008), Knee injuries and Osteoarthritis Outcome Score [KOOS] (Ross and Lohmander 2003) and Knee Self Efficacy Scale [K-SES] (Thomee et al. 2010). On the other hand, objective measures should take into account the factor of injury prevention and knee dynamic stability. The commonly used objective neuromuscular measures following ACLR surgery and subsequent rehabilitation include range of motion (ROM), anterior tibio-femoral displacement (ATFD) for knee laxity, rate of force development (RFD), electromechanical delay (EMD,) sensorimotor performance (SMP), proprioception and isokinetic peak forces for hamstrings and quadriceps musculature while functional knee performance tests include hop (vertical, horizontal and triple), figure of eight, shuttle run and stair climbing tests. As chapter five of this thesis suggested, the literature review had demonstrated negative or no correlation between the outcome measures of knee function, indicating that it is possible that each outcome measure might assess different aspect of knee function.

Neuromuscular performance indices such as muscular strength, peak force and torque have been widely reported in the scientific literature to have adequate characteristics of reproducibility and reliability (Minshull et al. 2007, Minshull et al. 2009, Gleeson et al. 2000). However many other indices related to neuromuscular performance of knee joint such as rate of force development, sensorimotor performance and electromechanical delay have received limited scrutiny in the latter characteristics. The examination of performance capability should be sufficiently precise in measurements in order to facilitate confident discrimination between performances (Gleeson et al. 2002).

Measurement precision is simply defined as the ability of a performance index to show the consistency when repeating a specific test protocol under the same environmental conditions (Denegar and Ball 1993). Achieving precise measurement requires a phase in which habituation takes place to eliminate systematic and statistically significant changes in performance scores while maintaining the same experimental conditions. The learning effect is normally indicative of lack adequate habituation phase and could interfere adversely with the proper assessment of measurement precision (Minshull et al. 2007, Gleeson et al. 2002). Habituation phase therefore allows attributing the changes observed in performance measurement to the biological variation or error within individuals as opposed to the carry over effects (i.e. learning effect). Given this fact, it is hypothesised that the less the variation or error in the performance scores, the greater reliability or reproducibility of measurement (Gleeson et al. 2007).

Measurement precision of test protocol in the current clinical evidence-based practice evaluates intra - session and inter - day sessions of performance capabilities. The intra-session reliability is concerned with comparing the changes of performance between contralateral and ipsilaterla limbs while inter-day reliability session is investigating the rate of this change over a period of time. They both allow facilitating confident discrimination between the performance capabilities (ref). In addition it allows estimating the number of replicates required for inter-and intra-day sessions in order to achieve the adequate measurement precision. For instance it has been shown that there is a subtle change (approximately 5%) of strength over the season within asymptomatic athletes (Minshull et al. 2009). Detecting the latter changes (i.e. small) requires the use of test protocol precise enough to discriminate such differences in the measurement. This hypothesis is relevant for clinical population (i.e symptomatic with soft tissue injuries requiring an intervention) who have subsequently experienced subtle but significant changes during the recovery period. The variability of intra-session estimates of neuromuscular performance is frequently used routinely for the contra-lateral limb comparisons in contemporary clinical practice (Gleeson et al. 2002, Minshull et al. 2007)

Reliability can be quantified using the intra- class correlation coefficient (RI) test along with the standard error of measurement (SEM) in order to separate the performance capabilities of individuals from within the group. RI is a parameter of reliability that advocates the measurement error and relates it to the variability observed between the individuals within population sample under study (de Vet et al. 2006). The typical formula for RI is obtained by dividing the true variance by the total variance as defined in the following expression:

$$\text{Reliability} = \frac{\text{Variability between study objects}}{\text{Variability between study objects + Measurement error}}$$

The ratio for RI ranges in value between 0 and 1 with 0 indicating a totally unreliable measurement while 1 representing perfect reliability

Another frequently reported measure for reliability coefficient index is the standard error of measurement [SEM] which distinctively defines different properties from the ICC (Stratford and Goldsmith 1997, Gleeson et al. 2002, Minshull et al. 2009). While the ICC contemplates the ability of a measure to discriminate among patients, SEM defines the magnitude of error of the measure being used. SEM is usually expressed by reporting the percentage (%) of the group mean value using the formula (SD x √ (1-RI) / mean) × 100 [multiplied by 1.96 to compute 95% confidence limits with the assumption of normal distribution of values] (Minshull et al. 2009, Feldt et al. 1985).

The current study in this chapter had chosen to include more than one outcome measures for knee function in order to assess the merit of each outcome measure. The following outcome measures had been selected for the assessment of knee function in the current study:

4.1.2 Outcome measures of knee (functional)

Single leg hop test

Of the very common functional tests for the knee joint are the hop tests including single leg hop, vertical hop and triple hop tests (Brand & Nylan 2009). It is important to emphasise here that functional knee tests are not designed to detect abnormalities surrounding the knee joint, but rather they are useful in assessing the capabilities of knee in tolerating safely stresses encountered in the joint as well as assessing indirectly knee pain which might inhibit functional task execution. Moreover, hop tests can indirectly assess the extent to which knee joint maintains its stability and necessary coordination with the muscles involved in action (Grindem et al 2011, Clark 2001). In addition, one of the main advantages of functional test is that they are fast, easy for staff to learn, simple to perform, and easy to conduct within clinical environment (Brand & Nylan 2009).

However, according to Lephart and Henry (1995), single leg hop test should be administered only if symptoms such as swelling, pain and crepitation are diminished and with knee demonstrating a complete and full extension and flexion range of motion. The single leg hop test involves take-off of one leg and landing on the same leg. Consequently, the latter test hold the advantage in that the uninjured leg can be ustilised as a reference guide for outcome from rehabilitation and in which the injured patient should achieve before determining his/her full return to physical activities. In addition, because single leg hop test allows testing the injured and uninjured leg separately, the test can therefore be used as a control to assess the discrepancy between the two limbs that may predispose re-injury (De Carlo & McDivitt 2006, Clark 2001). Although Goh & Boyle (1997) found that horizontal 6 and 12 meter single leg hop tests had strong association (rˆ0.62 ±0.75, P>0.05) with subjective assessment of knee function. In the absence of other inexpensive tool, hop still remains the most widely tool for quantification of knee function. One of the main advantages of the latter test is that it requires minimal time as well as minimal equipment to administer.

In terms of reliability, Bolgla and Keskula (1997) had reported an intra-class correlation coefficient for single leg hop test to be 0.96 and SEM of 4.56 cm when they examined the reliability of lower extremity functional performance in participants with no history of lower extremity problems. Reid et al. (2007) on the other hand investigated four types of hop tests (a 6-m timed hop, single hop for distance crossover hops for distance and a triple hop for distance) on 42 patients who had undergone ACLR surgery. Patients were tested on four occasions (the first occasion was for learning purpose, the second and third tests were recorded while the fourth test was used for validation purposes). The overall relative reliability (ICCs) for all 4 types of hop tests ranged from 0.82 to 0.93. Interestingly, the single hop test and overall limb symmetry index scores demonstrated the highest relative reliability. The ICC for single leg hop test were from while the limb symmetry index change scores for single leg hop test were 6.5% (at 95% CI; 4.5 – 8.5).

However, the standard error of measurement (SEM) for both the single hop test and limb symmetry index scores had been shown to be the lowest, indicating that the magnitude of error of the measure being used is high. In particular, the study of Reid et al. (2007) is deemed important as it is one of the first studies to contemplate the use of both SEM and minimal detectable change in the functional tests of knee performance. These two measures can play important role in determining the confidence clinicians can place in their assessment of patient's limb symmetry index for hop test. When looking at the overall hop test results of a particular patient, it is possible for instance to attribute the variations observed in symmetry index to the measurement error (SEM). The reliability results of the latter study are consistent with previous results of (Risberg et al. 1997, Booher et al. 1993, Shaw et al. 2005) with ICC ranging from 0.81 to 1.

IKDC

IKDC is becoming increasingly a popular assessment tool which incorporates subjective, physical and functional measures of knee joint integrity to arrive at a total performance score (Gleeson et al. 1998, Brand and Naylnad 2009). The primary aim of establishing IKDC was to develop and unify the standardised system of evaluating the results of knee in order to avoid the inconsistency and inaccuracy observed previously amongst different knee assessment scales (Anderson et al. 2006). Over the years, IKDC has been in constant revision in order to develop a more reliable and valid knee rating system (Collins et al. 2011, Higgins et al. 2007). The knee assessment form of IKDC is a self-reported functional outcome measure that consists of 18 questions measuring three main domains related to knee symptoms, function and sporting activity and daily living. The most recent version of IKDC is composed of six main sections; demographic form, current health assessment form, subjective knee evaluation form, knee history form, surgical documentation form and knee examination form.

In terms of reliability and validity, if Cronbach's alpha was at least 0.7, the internal consistency of the measure was said to be adequate while an intra-class correlation coefficient (ICC) of at least 0.8 for groups and test–retest (intra-rater) of 0.9 for individuals were also considered to be adequately reliable

(Collins et al 2011). The IKDC standard evaluation form for knee assessment has been shown to be a reliable, valid and responsive in terms of knee symptoms, function, and sports activity of patients with knee disorders including ligamentous injuries (Tow et al. 2005, Collins et al. 2011, Schmitt et al. 2010). In addition, the work of Schmitt et al. (2010) have found that IKDC is a valid with high internal consistency (Cronbach's alpha=0.93 and similar across all age groups) of knee-specific measure of function, symptoms and sports activity in participants between the ages of 6 and 18 years who presented different knee problems. In addition, Collins et al (2011) evaluated published reviews of several knee instruments and have shown that three studies (Padua et al. 2004, Crawford et al. 2007, Greco et al. 2020) had ICC ranging from 0.90 - 0.95 and SEM ranging from 3.2 – 5.6.

The Knee injury and Osteoarthritis Outcome Score (KOOS)

The Knee injury and Osteoarthritis Outcome Score (KOOS) inventory was chosen for the trials of this thesis because it was found to be more responsive for both short and long term knee conditions as compared to IKDC (Ross & Lohmander 2003). KOOS is an inventory that was designed to assess patient's perception about their knee and the short and long terms status of knee function and symptoms in patients suffering from knee injuries and osteoarthritis (Collins et al. 2011). The KOOS instrument has five distinctive subscales; pain, activities of daily living (ADL), quality of life related to knee (QOL) and function of sports and recreation (Sport/Rec). KOOS instrument allows determining the changes of function and symptoms that may occur in the knee joint over time. For instance, Nau et al. (2002) found that while IKDC showed no difference between a group who had BPTB graft and a group who had Ligament Advancement Reinforcement System (LARS) artificial ligament, the LARS group had shown better results in all the subscales of KOOS at one year follow up following ACLR surgery.

KOOS have been shown to be a valid inventory in assessing knee conditions that included ACL, knee osteoarthritis and meniscetomy (Roos & Lohmander 2003). In addition, test-retest reliability (ICC) of KOOS was reported for the sub-scales of pain, symptoms, ADL, Sport/Rec and QOL [0.83-0.93, 0.83-0.95, 0.75-0.91, 0.61-0.89 and 0.83-0.95, respectively] (Collins et al. 2011).

Lysholm knee scoring system

Lysholm knee scale was originally established to help orthopaedicians (physician-administered) measure the knee function of their patients following ACLR and other knee conditions (Briggs et al. 2009). However Lysholm scale has evolved in recent years to be a validated patient-administered instrument.

The scale is used to compare the pre-surgical scores with the follow-up scores to determine the rate of improvement in the knee functional domains. The questionnaire seeks to understand patient's perspective toward level of knee impairment and function in 8 sub-domains (limp, squatting, pain, swelling, stair climbing, locking, instability and support). However, one of the disadvantages of Lysholm is that it focuses on the short term consequences of knee condition (Briggs et al. 2009). Therefore, with the inclusion of KOOS and Lysholm in the trials of this thesis, a comparison can be made to assess the responsiveness of both instruments at the acute phases of ACLR rehabilitation.

The Lysholm score was reported to be reliable and valid having acceptable psychometric parameters of test-retest reliability, floor and ceiling effects, criterion validity, internal consistency (Paxton et al. 2003), construct validity, and responsiveness (Briggs et al. 2009). In his review on subjective measures of knee function, Collins reported that the ICC for 5 studies had ranged from 0.88 – 0.97 while the SEM ranged from 3.2–3.6 respectively.

The Knee Self-Efficacy Scale (K-SES)

Despite successful ACLR surgery and rehabilitation, some patients demonstrate inability to return to their pre-injury activity level. This could be due to lack of mental planning, health locus of control and their perception toward physical function. It is plausible therefore that patients who fail to return to pre-injury activity level, after the completion of what seems to be favourable rehabilitation, lack the psychological mental plan, low internal locus of control, goal-setting plan and a positive attitude during the rehabilitation regime (Thomee et al. 2006, Johnson 1996). Therefore, enhancement of high self-efficacy during rehabilitation through certain strategies may prove vital in acquiring a satisfactory outcome for ACLR patients.

First reported in 2006 by Thomee and his colleagues (Thomee et al. 2010), the Knee Self-Efficacy Scale (K-SES) is a psychometric measuring tool in which patients are able to assess their capabilities to organise or implement means of action that help them achieve prescribed types of performance. Bandura (1977) defined self-efficacy as one's ability to judge on how to carry out a task, rather than a measure of whether the individual is able to perform or not a particular task. One of the main advantages of using K-SES is the ability to determine the amount of individual's effort as well as the length of time of that effort when facing problems and challenges. In other words, the higher the self-efficacy demonstrated, the more likely it is for patients to demonstrate higher resolute in their efforts. In a model developed by (Brand and Nylan 2009), it is plausible to suggest that anxiety, patient commitment, depression, overall mood, self-efficacy, health locus of control and pain are important integrative psycho-biological influences that may contribute to patient's knee performance and outcome in the ACLR rehabilitation.

The developers of K-SES (Thomee et al. 2008) assessed 38 patients before and after 1 year following ACLR surgery using the following questionnaires; the Physical Activity Scale (a scale of 4-category with scores ranging from non-active to vigorous activity participation), Knee Injury and Osteoarthritis Outcome Score (KOOS), Tegner activity scale (a scale of 1-10 on physical and sport activity capability) and K-SES. When adjusted for Tegner pre-injury, gender and age, the pre-operative K-SES perceived future knee function score was found to be a significant predictor of a successful outcome after 1 year of ACLR surgery on the on KOOS [Sports and recreation] (P = 0.002, odds ratio = 1.6), Lysholm knee scoring scale (P = 0.003, odds ratio = 1.7) and KOOS [quality of life] (P = 0.037, odds ratio = 1.4). In addition, based on single leg hop test performance, the pre-operative K-SES knee function section score had been shown to predict significantly (P = 0.04, odds ratio= 2.2) the successful outcome at the 1 year follow-up. Given that K-SES assess the effort an individual is willing to expend in response to problems and calamitous event, it is plausible therefore to hypothesise that self-efficacy determines patient's interpretation about their knee symptoms and function, and how they relate their own behaviours to the outcome achieved after surgery.

K-SES has been shown to have acceptable reliability, validity and responsiveness within the literature (Thomee et al. 2008, 2010). However, given the fact that K-SES is relatively new instrument for knee assessment compared to KOOS, Lyhsolm and IKDC, it was hard to find enough evidence from the literature on the reliability and validity of this instrument. Most of the work of K-SES has evolved around studies conducted by the developer of K-SES (Thomee) and his colleagues. Nevertheless, Thomee et al. (2006) reported an internal consistency of 0.94 (Cronbach's alpha) for 22 items of K-SES. The scores of internal consistency for each section were 0.91 for sports activities, 0.94 for daily activities, 0.78 for knee function in the future and 0.92 for knee function activities.

It is worth mentioning that the study findings of Briggs et al. (2009) had concluded that the use of knee subjective questionnaires in isolation pose some limitations. Given these findings, it is plausible to suggest that using more than one questionnaire might enhance the overall finding of a particular domain within knee assessment questionnaires and subsequently investigate the correlations amongst them as an attempt to determine the outcomes that attribute to the successful rehabilitation of ACLR. Therefore this thesis will deploy IKDC, Lysholm and K-SES questionnaires in an RCT trial. In addition, an assessment of reliability of these questionnaires and correlation between them will also be offered in the trial of this thesis.

4.1.3 Objective measures of knee performance:

Knee laxity

Knee laxity, which refers to the increased anterior tibial translation, is the main reason for the episodes of anterior and rotary instability in the joint after ACL rupture. Stability of the ACLR knee plays a major role in forming the bases of which safe return of patients to pre-injury activity level is determined (Lam et al. 2009). In the late phases of rehabilitation, it is crucial that ACL reconstructed knee should demonstrate adequate stability while tested in similar on-field movements including cutting, landing from jump, deceleration and change of direction. Therefore evaluation of knee laxity using kinematics assessment provides unequivocally information that may form robust foundation of criteria for safe return to physical activity following ACLR rehabilitation (Lam et al. 2009).

The most commonly used physical examination for knee laxity include manual Lachman test, anterior drawer test, pivot shift testing and instrumented KT-1000 and KT-2000 arthrometer (Freedman et al. 2003, De Carlo and McDivitt 2006, Van Thiel and Bach 2010). Traditionally the KT-1000 test results are expressed in terms of the side-to-side difference in which the uninjured knee translation is subtracted from the injured knee with positive values representing increased knee laxity of the injured knee (Irrgang 2008). Although manual tests such as Lachman test was reported to be sensitive (0.85) and specific (0.95) as shown in a meta-analysis study of Benjaminse et al. (2009), the tests are deemed reliably unquantifiable. Therefore the use of the KT-1000 instrument was the preferred method of quantifying the anterior displacement of the injured ACL ligament. Indeed, the study results of Hanten et al. (1987) demonstrated that inter and intra-observer reliability were high with KT-1000 measurements in uninjured participants while Bach (1990) found excellent reproducibility in the anterior tibial displacement in 16 normal knees who were tested by one examiner. In fact Liu et al. (1985) had shown that KT-1000 and physical examination of knee joint had greater sensitivity in predicting ACL laxity than magnetic resonance imaging (MRI).

In reporting the scores of knee laxity, the manual Lachman test is classified into three main grades; grade 1 (mild); 1-5 mm, grade 2 (moderate); 6-10mm and grade 3 (severe); >10 mm. A value greater than 3 mm in anterior tibial translation compared with the other knee is considered a positive Lachman test, an indication of increased knee laxity (Biau et al. 2009). The KT1000 instrument scoring however uses another guidelines in which a side-to-side difference of 1 to 2 mm is deemed normal, 3 to 5 mm is deemed near to normal, 6 to 10 mm is deemed not normal while values higher than a 10 mm is regarded as severely abnormal (Irrgang 2008).

Muscular strength (quadriceps and hamstrings)

Maximum strength is defined as the highest voluntary force that can be generated under the influence of dynamic eccentric, dynamic concentric and isometric muscle action conditions, and is limited by recruiting specific muscle fibre and certain frequency of action potentials (Mebes et al. 2008). Along with passive stabilisers (e.g. ligaments, menisci and capsular structures), quadriceps and hamstrings are responsible for the dynamic stability of the knee joint (Tagesson et al. 2008), and optimal functioning of these stabilisers are crucial in both injury prevention and normal for functional and neuromuscular control (Risberg and Holm 2009, Fu et al. 2000). The capabilities of the active knee flexors and extensors have been traditionally estimated on the basis of peak force/torque parameters, 1 repetition maximum (1RM) and maximal voluntary contraction (MVC) performances. In particular, the knee flexor and extensor muscles are regarded as the main active stabilisers of the knee joint. However, as this thesis will discuss in the following chapters, the effectiveness of knee stabilisers are not predominantly determined by the absolute muscle strength. Factors such as rate of force development (RFD), electromechanical delay (EMD) contribute to the overall neuromuscular performance indices of the knee joint.

In an RCT study, Liu-Ambrose et al. (2003) ten participants were divided into two groups (strength training or proprioception training programmes) in which they had to follow their protocols for 12 weeks during ACLR rehabilitation programme. Although both groups showed a significantly similar gains in subjective measures (Lysholm, Tegner and Gillguist activity scales) and functional performance [hop test] ($p<0.01$) following their 12 week training protocol, the results demonstrated that the strength of quadriceps (isokinetic torque) was a determinant for functional performance in the ACLR reconstructed limb ($r^2= 0.72$). However this study lacked the power to detect meaningful difference in both subjective and functional performance scores as it included only 5 participants in each group.

One the most commonly used instrument in the measurement of muscular peak forces/torques is isokinetic dynamometry. The latter dynamometry has been extensively used in many studies for the assessments of neuromuscular performances (muscle peak forces/torques, EMD and RFD) and sensorimotor performances (force and positional errors) and is similar to the one used in the prospective trials of this thesis. In term of the reliability of isokinetic dynamometry, Gentil et al. 2011 assessed the isokinetic peak torque of the knee extensor and found that test and retest ICC and standard error of the mean (SEM) were 0.98 and 2.3 % respectively. In addition, Risberg and Holm (2009) had shown high reliability in using Isokinetic muscle strength tests with intra-class correlation coefficients ranging from 0.81 to 0.97.

Rate of force development (RFD)

There is very little in the literature regarding the use of electromechanical delay (EMD) and rate of force development (RFD) as important outcome measures for determining patient's progress, recovery and ultimately readiness to full return to pre-injury level. RFD (N/second) can be defined as the slope of the force-time curve that occurs under isometric conditions of muscle contraction (Aagaard et al. 2002). In other words RFD describes the ability for fast force generation of muscle. The relevance of this outcome measures lies on its association to the normal daily life activities such as walking and stair climbing which are based on specific strength requirements. Although such activities are categorically slow and undemanding, recent studies assessing the ground reaction forces (measured with force plates) demonstrated that generating high and fast force developments are crucially important for these activities (Mebes et al 2008). RFD measured under isometric contractions has been acknowledged as a key parameter characterizing the extent of neural drive to the muscle during rapid maximal muscle actions (Angellozi et al 2012). The inclusion of this variable therefore might contribute to the robustness of the criteria used in determining patient's readiness to resume normal daily and functional activities. For instance, one of the criterion for assessing someone's readiness is the ability to reach at least 80-85 % of the maximal strength of the uninjured knee side. In terms of explosive muscle actions, the duration of activating maximal muscle strength (300 milliseconds) is longer than the duration required for muscle to develop muscular strength (0-200 milliseconds) in either daily functional activities or sporting activities (Angellozi et al 2012). This indicates that RFD play more important role in muscle function than maximal muscle strength. On the basis of these findings, RFD has therefore been used extensively to evaluate the capacity of generating muscular force at a rapid rate. Such evaluation is considered an essential component of functional tasks including postural balance as well as sports performance (Aagaard et al. 2002). For instance, it has been reported that a value of 150–300 milliseconds is required to reach weight acceptance on a single during walking, a point where peak forces might be almost 1.2 times the body weight. Therefore shorter times and higher loads are expectedly reported in during sports activities. If delayed, the shorter time required in RFD for muscular contraction may have serious consequences and compromises the stability of joint which ultimately contribute to the cause of neuromuscular injury (Mebes et al 2008).

Oliveira et al. (2013) carried out a study in which he and colleagues examined the effects of a 6-week isometric resistance training aimed at improving explosive and maximal strength on RFD varying from 10 to 250 milliseconds from the contraction onset. The results demonstrated that both very early and late phases of RFD had different responses following the short resistive training prescribed. The resistive training prescribed has relatively induced gain in early phase of RFD and maximal voluntary contraction whereas the late phase of RFD remained unchanged. In another study, Angellozi et al (2012) concluded that after 6 months of ACLR rehabilitation, RFD had only reached 63% of pre- injury level, whereas at 12 months RFD attained 90% of pre-injury level. Based on the later study, it is fair to assume that it takes about a year to reach the full pre-injury status of RFD, a finding that could have an important implication into the current practice of ACLR rehabilitation and time frame required to declare someone's readiness to resume his/her daily physical activities.

With regards to reliability of RFD, Minshull et al. (2009) had had compared the intra-class correlation (RI) and V% of RFD in magnetically evoked and volitional knee performance on 12 healthy adults. The results demonstrated RI reliability ranging from 0.81 ± 0.09, 20.6 of V % and SEM of 24.5 %.

Electromechanical delay (EMD)

Similar to RFD, there is limited published work in the literature which regards electromechanical delay as potentially an important variable that might determine the successful outcome measures of ACLR rehabilitation. In the physiology of muscle, a delay exists between the onset of muscle tension and electrical activity during the contraction of skeletal muscle. This is namely called electromechanical delay (EMD), and can be defined as the time between the tension in skeletal muscle and the onset of electrical activity (Zhou et al. 1998). EMD is linked with the propagation of the action potential through the muscle and through a series of excitation-contraction coupling that result in the stretching of series elastic component of muscle, an important component which might lead to a better understanding of musculoskeletal performance of a joint system (Gleeson et al. 2008). As a neuromuscular performance and a component of the stretch reflex, EMD can play an important role in neuromuscular reaction time which is required during forces of unrestricted development and sufficient magnitude capable of damaging ligamentous tissue in synovial joints (Gleeson et al. 2005). A typical example that illustrates the importance of EMD is in the case of ACLR surgery. After the surgical intervention of harvesting muscle patellar tendon for graft in the ACL reconstruction, scar tissue develops around the graft-harvested area. It has been hypothesized that the scar tissue development might prolong the reaction time of muscles fibres to sudden stimulus, namely called electromechanical delay (EMD). This prolonged reaction time to stimulus is believed to be due to two main factors 1) impaired proprioception in knee joint after ACLR surgical intervention and 2) greater elasticity in series elastic component of the quadriceps femoris (in the case of harvesting patellar tendon) and prolonged processing interval in central nervous system (CNS).

The normal delay's ranges of EMD have been stated to be between 30 and 100 milliseconds (Cavanagh and Komi 1979). In a study by Cavanagh and Komi (1979) EMD values were investigated through forearm flexion-extension cycles of 135 degrees at an angular velocity of ~ 0.5 rad/s. The mean value for the delay in eccentric activity was (49.5 milliseconds) and was found to be significantly different ($p < 0.05$) from the delays during isometric (53.9 milliseconds) and concentric activity (55.5 milliseconds). However, this delay is expected to be much shorter in the case of rapid movements. For instance, in one study Norman and Komi (1979), reported the values of 25-45 milliseconds of EMD in the forearm muscle movement. Relevant to the ACLR surgery, it remains unclear yet as whether the graft harvested area can demonstrate changes to the EMD of the knee extensor muscles (in the case of patellar tendon graft) or not. With fact that scar tissue has different biomechanical characteristics, there remains a possibility of developing alterations in the elastic properties of the harvested graft area (tendon) that might ultimately lead to differences in the stiffness of the series elastic components of the knee extensor muscles (Georgoulis et al. 2005).

A recent study by Georgoulis et al. (2005) demonstrated that no significant changes for the maximal voluntary contraction (MVC) of the knee extensors and for the EMD of the Rectus Femoris and the Vastus Medialis muscles due to the development of patellar scar tissue on patients who underwent Bone-Patella-tendon- Bone graft ACL reconstructive surgery, an indication that scar tissue development has no effect in changing or altering the stiffness of the patellar tendon to an extent that could result in EMD alterations. However, in a study by Ristanis et al. (2009) on patients who had ACLR rehabilitation following Semitendinous/Gracillis (ST/G) graft, a significant elongation of the EMD of the hamstring muscles was found. This finding indicates that the scar tissue development in the graft-harvested area had an effect (prolongation) on EMD of hamstrings while here was the lack of effect of EMD on patellar tendon graft harvested area in the study of Georgoulis and his colleagues.

The evidence of reliability of EMD within literature is very limited. To the best knowledge of the researcher, only one study had reported the reliability and the reproducibility (defined earlier as the coefficient of variation (V %) represented as a percentage of the mean group score) of EMD. Minshull et al. (2002) had compared the intra-class correlation (RI) and V% of EMD in magnetically evoked and volitional performance of knee flexors and extensors on 12 healthy adults. The results demonstrated RI reliability ranging from 0.98 – 0.64 and V% ranging from 3.7 – 25.2%, while the evoked indices demonstrated a relatively lower reliability scores (RI: 0.98–0.51), V% ranging from 4.3 – 31.2% and SEM of 10.8 %.

4.1.4 Research Aims

In summary, while the systematic review of chapter two have shown that some studies had demonstrated clinical efficacy of accelerated conditioning during ACLR rehabilitation, the latter studies had not quantified the increased frequency, intensity and time of exercise stress associated with the accelerated rehabilitation programme. The current RCT study, however, had investigated the clinical efficacy of quantified accelerated conditioning and whether or not it offers superior rehabilitative outcomes or long-term stability than that demonstrated in contemporary rehabilitation. The aims of this RCT trial were therefore to:

Primary Aim

- Investigate the effects of accelerated conditioning [increased frequency and intensity of exercise stress associated with introducing early weight bearing, range of motion] on the primary objective functional outcome [single leg hop test] and primary subjective patient-reported measures [IKDC, KOOS, K-SES and Lysholm] in a clinical population undergoing knee rehabilitation following ACLR surgery (BPTB and hamstring grafts).

Secondary Aim

- Investigate the effects of accelerated conditioning [increased frequency and intensity of exercise stress associated with introducing early weight bearing, range of motion] on the secondary objective neuromuscular outcomes (peak force [PF], electromechanical delay [EMD], rate of force development [RFD], sensorimotor performances [SMP] in a clinical population undergoing knee rehabilitation following ACLR surgery (BPTB and hamstring grafts).

- Investigate the influence of anthropometric and orthopaedic-related factors on the outcomes of knee function following ACLR surgery.

4.1.5 Research Hypothesis

Hypothesis one

- Null (*Ho*): There will be no effect of accelerated conditioning [increased frequency and intensity of exercise stress associated with introducing early weight bearing, range of motion] on the primary functional outcomes (single leg hop test, IKDC, KOOS, K-SES and Lysholm) in a clinical population of knee ACLR rehabilitation.

- Alternative: There will be an effect of accelerated conditioning [increased frequency and intensity of exercise stress associated with introducing early weight bearing, range of motion] on the primary functional outcomes (single leg hop test, IKDC, KOOS, K-SES and Lysholm) in a clinical population of knee ACLR rehabilitation

Hypothesis two

- Null (*Ho*): There will be no effect of accelerated conditioning [increased frequency and intensity of exercise stress associated with introducing early weight bearing, range of motion] on the secondary objective neuromuscular outcomes (PF, EMD, RFD, SMP performances) in a clinical population of knee ACLR rehabilitation.
-
- Alternative: There will be an effect of accelerated conditioning [increased frequency and intensity of exercise stress associated with introducing early weight bearing, range of motion] on the secondary objective neuromuscular outcomes (PF, EMD, RFD, SMP performances) in a clinical population of knee ACLR rehabilitation.

Hypothesis three

- Null (*Ho*): There will be no influence of anthropometric and orthopaedic-related factors on the functional and objective neuromuscular outcomes of knee in a clinical population of knee ACLR rehabilitation.

- Alternative: There will be an influence of anthropometric and orthopaedic-related factors on the functional and objective neuromuscular outcomes of knee in a clinical population of knee ACLR rehabilitation.

4.2 Method

4.2.1 Patients' recruitment

Potential participants were identified using special hospital software that allowed the access of patient's' data. Five consultant orthopaedic surgeons (PG; SR; AB; SW, RR) of similar experience and practice (> 12 ACL reconstruction surgeries per month) using agreed and matched surgical procedures were happy to be involved in this study. Patients who had consented for ACL autologous reconstructive surgery by one of the five surgeons involved in this study and who would be willing to attend Robert Jones and Agnes Hunt (RJAH) Orthopaedic and District Foundation Trust for rehabilitation were approached through phone calls and emails. On their last orthopaedic appointment prior to surgery, potential participants were informed of study's objectives and aims, including the potential risks and benefits and Patient Information Sheet and Informed Consent Form were issued (see Appendix I for Patient Information Sheet and Appendix II for Informed Consent Form). The participants were then contacted approximately one week after the initial meeting and were given the opportunity to ask further questions. All participants were fully aware that they could withdraw from the study without giving any reason and this would in no way alter the care they received. The study was approved by the Ethics Committee of the Shropshire area NHS Ethics Committee: REC reference 11/WM/0417 (Appendix III).

Patients meeting inclusion criteria from a date specific and randomly-sequenced cohort awaiting surgery or subsequently presenting with injury were offered participation. No exclusions were made regarding the autologous graft choice. No exclusions were made on the basis of gender or race. Only patients over 16 years old who were deemed musculoskeletally and mentally mature were invited to take part in the study. Patients suffering with bilateral knee pathologies at the time of consent were excluded as the contra-lateral knee would not suffice as a control. Multiple ligament injuries that would require adaptation to the standard rehabilitative practice were excluded. Patients with systemic conditions such as rheumatoid arthritis, chronic obstructive airways disease or cardiac pathology were excluded on the basis that their physiological responses to training would be compromised and their physical ability to take part in the rehabilitation programmes investigated in this study would prove difficult and clinically inappropriate. In summary, the following inclusion and exclusion criteria were used for the study.

4.2.2 Inclusion criteria:

- Adults over 16 years of age and mentally mature
- Listed for ACL reconstructive surgery following informed surgical consent
- Patients were under the care of one of two surgeons identified to perform the surgery
- Autologous graft tissue; either central third bone-patella- tendon-bone (BPTB) or semitendinosus and gracilis from the ipsilateral leg.
- Agreed to attend RJAH Orthopaedic Hospital for post-operative rehabilitation
- All ethnic groups
- Male or Female

4.2.3 Exclusion criteria:

- Patients with systemic pathologies
- Bilateral knee injuries at the time of consent
- Multiple ligament injuries to the knee
- Declined to participation in the study

Out of 70 patients contacted for this trial, 55 showed their willingness to participate in this trial. However, the final number of patients who participated in this study was reduced to forty patients of which 17% (6 participants) were lost during follow-up. Figure 4.1 illustrates the consort diagram that included the number of excluded patients, lost to follow up, intention to treat (ITT) of this trial. Forty adults [men, 34 women, 06; (mean ± SD), age 32.23 ± 12.27 years, 29.60 ± 11.61; height 1.76 ± 0.04, 1.62 ± 0.04 m; body mass; 80.25 ± 9.63, 64.24 ± 8.9 kg] electing to undergo unilateral ACL-reconstructive surgery (central third BPTB graft, or semitendinosus and gracilis graft) at a RJAH, Oswestry, U.K. National Health Service Foundation Trust hospital gave their informed consent to participate in the study.

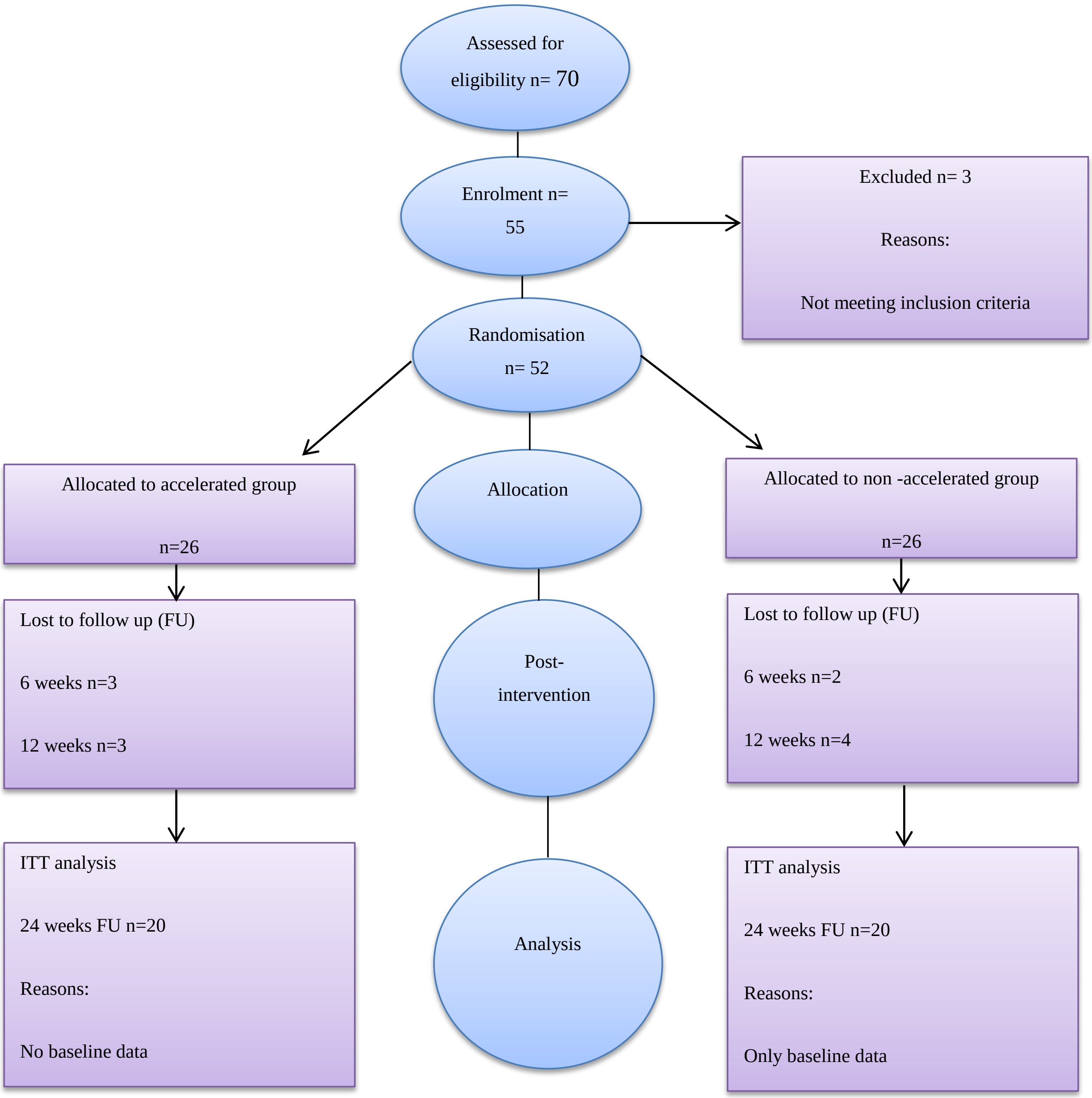


Figure 4.1 CONSORT (Consolidated Standards of Reporting Trials) flow chart of the study, including intention-to-treat (ITT) analysis.

4.2.4 Participant's characteristics

No statistical group (experimental; control) differences ($p>0.05$) in terms of anthropometric characteristics (with means ± standard deviations) of age, body mass, BMI, height, and orthopaedic-related factors (unstructured physical activity and compliance [number of visits] and waiting time) was observed (Table 4.1). Therefore the two groups had been considered "well-matched" on the main variables of anthropometric characteristics.

Patients who had BPTB graft were 8% while the remaining 92% of patients had hamstring graft. All participants had been previously involved in either recreational or non-professional sports activities. Sixty four percent (64 %) of patients had presented with right knee injury and seventy four percent 74.2% of patients had reported that injury occurred to their preferred leg. Sixty two percent (62%) of patients had reported that injury occurred due to non-contact mechanism during sports activities, twenty four percent (24%) due to normal activities of daily living and fourteen percent (14%) due to contact injury mechanism. The mechanism of injury was therefore categorised as either 'non-contact' or 'contact' in which 'contact' mechanism was defined as an injury that occurred due to contact with another player and consequently resulted in ACL injury, regardless of where on the body the contact had actually occurred. Patients were sequentially batch-allocated randomly to groups (experimental; control). Using computerised random number generator software, patients were prospectively randomised into two groups:

Control (Contemporary) group: (n=20 [15♂, 5♀ [age: 32.3 ± 2.9 yr (range 18 to 64 yr); height = 174.2 ± 1.51 cm; body mass = 78.0 ±2.36.0 kg; time from injury to surgery 202.5 ± 25.9 weeks]; compliance (visits to rehabilitation) = 14.4 ± 1.1 sessions (range: 9 to 25); n=6 lost to follow-up] contemporary rehabilitation consisted of a standardised and supervised programme of ACLR rehabilitation used currently in the clinical practice of 24 weeks focusing on progressive strength, mobility and endurance conditioning.

Experimental (Accelerated) group: (n=20 [19♂, 1♀ [age: 31.2 ± 2.3 yr (range 18 to 50 yr); height = 175.3 ± 1.49 cm; body mass = 78.4 ± 2.54 kg; time from injury to surgery 8.3 ± 6.7 months]; n=6 lost to follow-up] accelerated rehabilitation comprised the specific phasing of accelerated conditioning with increased frequency and intensity of exercise stress associated with early introduction of weight bearing, ROM and quadriceps isometric and OKC exercises in the accelerated group.

Table 4.1: Means of age, body mass, BMI, height, unstructured physical activity and visits to physiotherapy sessions for both groups. F ratios and p values for one way ANOVA comparisons between the two groups are reported.

Variable		N	Mean	SD	F	Sig.
Age (year)	Accelerated	20	31.2	10.5	0.08	0.77
	Contemporary	20	32.3	13.3		
Height (cm)	Accelerated	20	175	7.6	0.26	0.60
	Contemporary	20	174	6.7		
BMI	Accelerated	20	24	2.7	0.04	0.07
	Contemporary	20	27	2.4		
Visits (sessions)	Accelerated	20	14.4	4.2	0.00	1.00
	Contemporary	20	14.4	5.0		
Waiting time (months)	Accelerated	20	202	116.1	2.88	0.06
	Contemporary	20	126	166.4		
Unstructured physical activity [pre-surgery] ($Kcal \cdot day^{-1}$)	Accelerated	20	219.2	103.6	0.69	0.40
	Contemporary	20	157.5	65.8		
Unstructured physical activity 12 weeks post-op ($Kcal \cdot day^{-1}$)	Accelerated	20	226.7	138.7	1.28	0.26
	Contemporary	20	189.3	50.8		
Unstructured physical activity 24 weeks post-op ($Kcal \cdot day^{-1}$)	Accelerated	20	335.5	208.6	0.14	0.70
	Contemporary	20	385.8	543.5		

Key: PA: Physical activity. SD: Standard deviation.

4.2.5 Experimental design

Assessment procedures

This was a RCT study comparing the clinical efficacy and effects of a novel post-surgical rehabilitation comprising accelerated rehabilitation conditioning with control (contemporary) rehabilitation on knee function and neuromuscular outcome measures in patients who underwent ACLR surgery. After surgery, all patients were treated by four physiotherapists for the entire duration of their rehabilitation programme. Physiotherapists treating accelerated group were instructed to prescribe the accelerated conditioning programme while those treating control group were instructed to prescribe contemporary rehabilitation programme. Both programmes of ACLR rehabilitation are mentioned in full details later in this method section. The experimental design comprised a longitudinal comparison of performances associated with the leg undergoing surgery with those of the contralateral control limb during the phases of recovery. Patients were assessed on four separate occasions pre-surgery (0 weeks), at 6 weeks, 12 weeks, and 24 weeks post-surgery). The timing of post-surgery testing occasions (6, 12 and 24 weeks post-surgery) were chosen based on the evidence that the latter occasions are best reflecting the most rapid period in which physical improvement and effect sizes during the rehabilitation process are observed (Ardern et al. 2011). Moreover, physiotherapists are routinely evaluating patient’s status during the mentioned occasions in order to determine patient’s progress in ACLR rehabilitation (De Carlo and McDivitt 2006).

In brief, the first assessment session included time for patients to become familiarised with the assessment procedures and protocols and was devised to obtain pre-surgery measures of knee stability and performance and perceived knee function. During this initial meeting with the researcher (~2 weeks pre-surgery) and at subsequent assessment sessions (conducted at 6 weeks, 12 weeks and 24 weeks) following surgery, each patient was assessed for primary outcomes of function [single-leg hop, Lysholm, K-SES, and KOOS, IKDC] together with secondary objective neuromuscular (anterior tibio-femoral displacement (ATFD), peak force (PF), electromechanical delay (EMD), rate of force development (RFD), and sensorimotor performance (SMP) associated with the knee extensors (quadriceps) and flexors (hamstrings) of the injured and non-injured legs. Assessments and the order of testing legs were undertaken in a random sequence. While these indices of objective neuromuscular measures (ATFD, PF, RFD, SMP and EMD) would not be readily available within contemporary clinical practice, their inclusion might allow an understanding of neuromuscular performance during recovery and rehabilitation following ACL surgery (Gleeson et al. 2005, Minshull et al. 2009). Prior to all testing, patients undertook a standardised warm-up protocol that involved five minutes of cycle ergometry (60 watts for females, 90 watts for males provided clinically tolerable by patients). This was followed by static stretching (five minutes) of the involved limb. The protocol design of this trial is illustrated schematically in Figure 4.6.

Dynamometer orientation and participants

Patients were secured in a seated position on a custom-built dynamometer (Minshull at al. 2009) [Figure 4.2]. Gleeson et al. (1992) have shown that this device is a reliable and valid means of knee joint assessment. The dynamometer's lever-arm was attached to each leg using padded ankle-cuffs and strapping that are fixed proximal to the lateral malleolus. An alignment was established between the dynamometer and the knee joint's axes of rotation. Adjustable strapping across the mid-thoracic spine, pelvis and posterior thigh proximal to the knee localised the action of the involved musculature. Based on the information from literature on the greatest mechanical strain on key ligaments (Li et al. 1999), a functionally relevant knee flexion angle of 25 degrees (0.44 rad), (0° = full knee extension) was identified for each patient during activation of the involved musculature using a goniometer system and was maintained throughout testing.

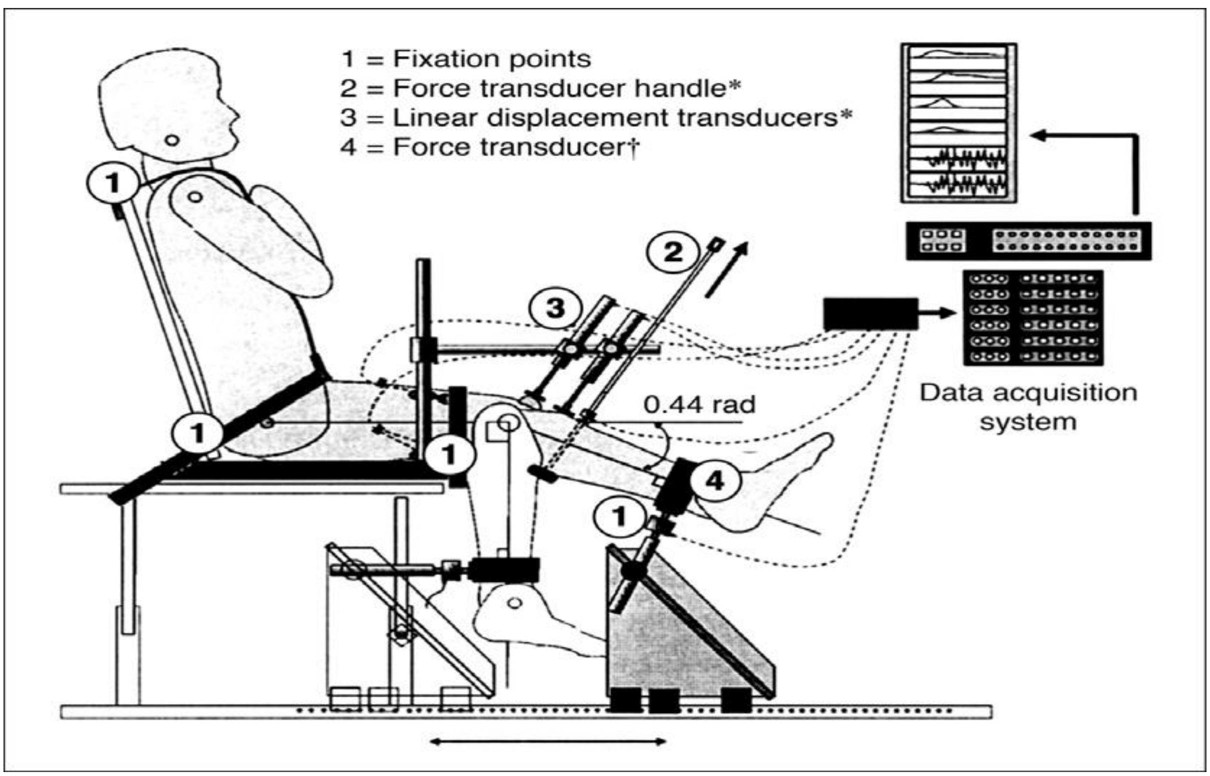


Figure 4.2: Schematic illustration of participant and dynamometer orientation (adapted from Gleeson et al. 2008)

Prior to participant orientation on the dynamometer and neuromuscular assessments, rigorous skin preparation including shaving, abrading (using fine sand paper) and de-greasing (using an alcohol swab) of the skin over the belly of the biceps femoris was undertaken. Two self-adhesive bi-polar surface electrodes (AgCl) were placed equidistant from the ischial tuberosity and the medial epicondyle of the femur with a fixed inter-electrode distance of 30 mm apart on both the injured and non-injured limbs. The m. biceps femoris and m. vastus lateralis were selected as important contributors and implicated in ACL injury (Li et al. 1999). A third or 'reference' electrode was placed 30 mm lateral and equidistant from the recording electrodes parallel to the gap between the two detector electrodes. Electrode placement was standardised across assessment occasions, where appropriate, by means of mapping (using acetate paper) and measuring the position relative to anatomical landmarks. Skin preparation quality was assessed using an impedance meter with a resistance of less than 5 KΩ being acceptable (Basmajian et al. 1985). Feedback of results was not given to patients until after they completed the prescribed number of test occasions.

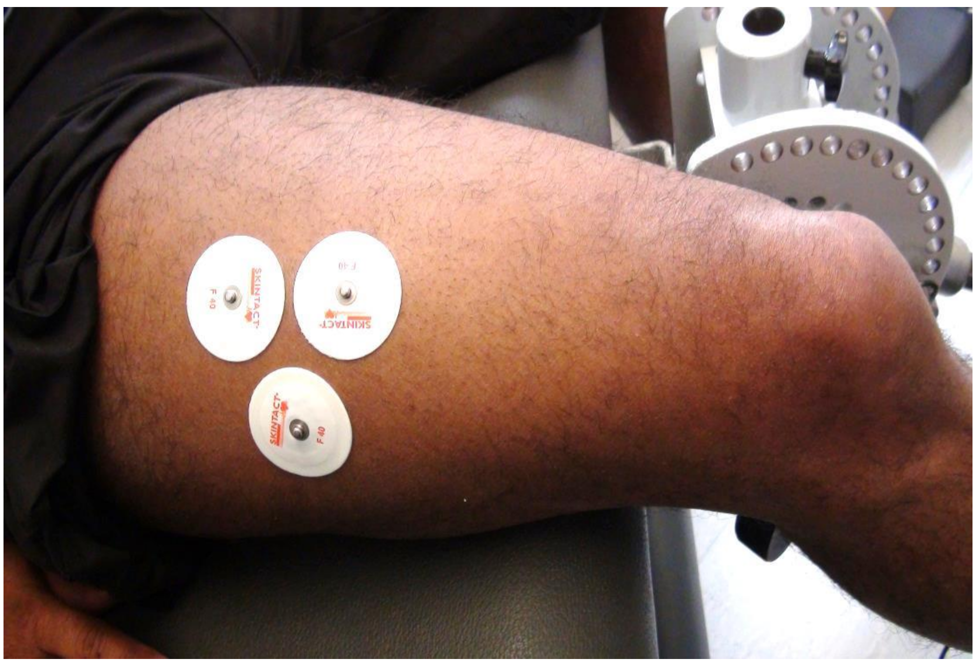


Figure 4.3: The placement of electrodes for recording electromyographic (EMG) activity. The two electrodes are placed on the equidistant from the ischial tuberosity and the medial epicondyle of the femur with a fixed inter-electrode distance of 30 mm between them. The third electrode "a reference electrode" is placed 30 mm lateral and equidistant from the recording electrodes parallel to the gap between the two detector electrodes.

Rehabilitation protocols:

Accelerated rehabilitation

The experimental (accelerated) group was prescribed a rehabilitation programme that had different milestones compared to that of contemporary group. In principle, full weight bearing, ROM, leg curl, seated leg press, isometric and OKC for quadriceps associated with increased frequency and intensity of exercise stress were performed earlier in the accelerated group than the contemporary group. Additionally, based on Beynnon et al. (2011), any exercise that are thought to increase ACL strain values (e.g. squatting with increased external weight) were introduced earlier in the accelerated rehabilitation while exercises causing no increase in ACL strain were started simultaneously in both programmes. For instance, while the full weight bearing was achieved in week 2-4 in the contemporary group, the accelerated group were guided to achieve the latter by day 10 post-operatively. Isometric OKC quadriceps ($90-45^0$ knee flexion range) was started by day 10 post-operatively in the accelerated group while the latter exercise was delivered later (3 weeks post-surgery) in the contemporary group. Another example is that accelerated group were instructed to achieve 90^0 knee flexion by week 2 while for contemporary group the latter ROM was achieved between weeks 4-6. Further examples of the key differences in the early, intermediate and late phases of rehabilitation between the two groups are shown in Table 4.2.

Contemporary rehabilitation

The early acute stage (1-6 weeks post-surgery) of ACLR rehabilitation comprised standard rehabilitation exercises concentrating on gaining terminal knee extension ROM in the injured knee, gait re-education, static cycling, , step-ups, active and resisted exercises of the upper body, core stability and proprioceptive activities. During the sub-acute stage (6-12 weeks post-surgery), proprioceptive work was increased, resisted exercises (with the exception of through range open-kinetic-chain extension for quadriceps) were introduced and other moderate activities such as one-legged dips and step-ups were increased. Early plyometric exercises were added and included jumps, leaps and hops in partial-weight bearing scenario using a set of parallel bars in-front of a mirror to correct any biomechanical errors. During the late phase of the rehabilitation (12-24 weeks post-surgery), emphasis was increased on dynamic neuromuscular training that involved plyometric and agility drills. Eccentric quadriceps control was established via interval treadmill walk, jog was added, progressing direction, full-weight bearing double leg jumps on the spot was progressed to travelling forwards, backwards, sideways, 180° rotations and jumping from a step, advancing to single leg work. From approximately week 16 predictable twisting/turning agility circuits were added under the physiotherapy supervision and from week 20 unpredictable sports specific agility training on the sports field was subsequently included. This naturally progressed to contact sport training from week 24 and a graduated return to all sporting activity thereafter.

Frequency, Intensity and Time (FIT) of exercises in accelerated and contemporary groups

From 12 to week 24 post-surgery (mid to late stages of rehabilitation), participants in both groups performed the same dosage (frequency, intensity and time) of exercises conditioning (Table 4.2), proprioceptive, plyometric and cardiovascular training. For further details on the shared exercise programme between the two groups from week 12 to 24, please refer to Appendix V). Therefore, the overall FIT of exercises conditioning was higher in the accelerated than that of contemporary group at the acute and sub-acute phases due to the increased frequency and intensity introduced the latter phases. Example of the differences in frequency and intensity of exercises conditioning prescribed for the controls and the experimental groups are shown in Table 4.4.

Post-op period	Contemporary	Accelerated
Day 1- week 1	Cryotherapy. Gain terminal extension No brace CPM. Passive flexion Knee flexion initiated (day 1-3)	Cryotherapy. Gain terminal extension No brace CPM. Passive flexion Knee flexion initiated (day one), Isometric static quads
Day 10 - week 12	FWB (week 2-4) 90 flexion (week 4-6) Mini Squat (week 2) Isometric OKC quadriceps 90-45 range (week 3) CKC (quadriceps), OKC and OKC (hamstrings) Hydrotherapy (breast stroke by week 14) Example on reps, sets, external weight of quadriceps and hamstring with frequency and intensity of exercises for contemporary see Table 4.4	FWB (day 10) 90 flexion (week 2) Mini Squat (day 7) Isometric OKC quadriceps 90-45 range (day 10) OKC, leg curl, seated leg press and OKC and OKC (hamstrings) Hydrotherapy (breast stroke by week 12) Example on reps, sets, external weight of quadriceps and hamstring with increased frequency and intensity of exercises for accelerated group see Table 4.4
From week 12	Proprioceptive training Jogging, Running Same FIT exercise stress Progress to incorporate: agility, run/ sprint/cut/ pivot/ accelerate/ decelerate	Proprioceptive training Jogging, Running Same FIT exercise stress Progress to incorporate: agility, run/ sprint/cut/ pivot/ accelerate/ decelerate
From week 15	Non-contact training Non-contact sport	Non-contact training Non-contact sport
From week 24	Symptom free training No residual complications Psychologically prepared	Symptom free training No residual complications Psychologically prepared

Keys: FWB: full weight bearing. OKC: open kinetic chain. CKC: closed kinetic chain. CPM: continuous passive motion. FIT: frequency, intensity, time.

Table 4.2: Based on evidence-based recommendations (Van Grinsven et al. 2010, Risberg et al. 2004, Shelbourne et al.1992), accelerated rehabilitation emphasises on earlier recovery of quadriceps strength, ROM, and weight bearing where clinically possible. However, the early introduction of exercises (e.g. isometric and OKC of quadriceps work) in the accelerated group was not purposely as early as the one endorsed in the literature by Van Grinsven et al. (2010) and Beynnon et al. (2005). For instance the latter authors endorsed isometric OKC quadriceps work 7 days after surgery compared to 10 days after surgery in the trial of this thesis. The conservative approach taken in this study was thought to minimise any excessive ACL strain that exercises might cause for patients. The key difference between the two groups is the period from day 10-week 12 post-operatively.

Week (post-op)	Exercise	Accelerated group	Contemporary group
Week 6	Leg curl	20 rep *3 set * 4 kg	10 rep *2 set * 2 kg
	OKC Leg extension	20 rep *3 set * 4 kg	10 rep *2 set * 2 kg
	Squat	20 rep *3 set * 4 kg	10 rep *2 set * 2 kg
	Seated leg press	20 rep *3 set * 4 kg	10 rep *2 set * 2 kg
Week 7	Leg curl	20 rep *3 set * 6 kg	15 rep *3 set * 2 kg
	OKC Leg extension	20 rep *3 set * 6 kg	15 rep *3 set * 2 kg
	Squat	20 rep *3 set * 6 kg	15 rep *3 set * 2 kg
	Seated leg press	20 rep *3 set * 6 kg	15 rep *3 set * 2 kg
Week 8	Leg curl	30 rep *3 set * 8 kg	20 rep *3 set * 4 kg
	OKC Leg extension	30 rep *3 set * 8 kg	20 rep *3 set * 4 kg
	Squat	30 rep *3 set * 8 kg	20 rep *3 set * 4 kg
	Seated leg press	30 rep *3 set * 8 kg	20 rep *3 set * 4 kg

Table 4.3: Example of the differences in strength conditioning (repetition*set*weight lifted) prescribed for the controls and the experimental group. Based on Beynnon et al. (2011), accelerated rehabilitation introduces exercises that are thought to increase ACL strain values earlier (e.g. contraction of the quadriceps muscles with increased external weight) while exercises causing no increase in ACL strain were started simultaneously in both programmes.

4.2.6 Minimal clinically important difference (MCID)

The term “minimal clinically important difference” (MCID) was first introduced by Jaeschke and colleagues in 1989 on the grounds that although the use of assessment tools might determine statistical significant changes following intervention, these changes might not necessarily represent clinical relevance and importance to both clinicians and patients (Cook 2008). Therefore, the term “MCID” has been recently used to separate what is deemed clinically important from that of no clinical importance (Collins et al. 2011). Greco et al. (2010, pp. 894) defined minimal clinically important difference as “the change score that serves as the optimal cut-off point for discriminating individuals who perceive themselves to be improved from those who do not”. Obtaining the values of MCID of an assessment tool helps clinicians to obtain the confidence of the assessment tool used (Reid et al. 2007). For instance, Collins et al. (2011) determined MCID of knee function using patient-reported outcome measures including KOOS, IKDC and Lysholm, and concluded that the cut-off points that discriminate those who thought “had improved” from those who thought “had not” represented meaningful changes to the patient. Relevant to patient-reported outcome measures, Irrgang et al. (2006) had reported 11.5 unit score as an MCID cut-off point when using IKDC. On the other hand, Roos and Lohmander (2003) investigated the MCID for KOOS questionnaire and identified that a change score of 8 points indicate a clinically significant difference between the those who clinically “improved” and those who “did not”. Although MCID relies primarily on patient’s perception, a review of literature revealed variations in the methods used for determining MCID. For instance, some reported the use of clinician’s report and clinical effectiveness of intervention (effect sizes) in the attempt of determining meaningful changes for the patients. An MCID for knee laxity and knee flexion angle were reported to be 3mm and 3.5^0, respectively (Di Stasi et al. 2012). A loss of more than 3.5^0 knee flexion angle (i.e. MCID) had shown to have adverse effects on patient-reported and objective measures in the study of Shelbourne and Gray (2009). This variation and lack of consensus in the methods used for MCID has caused methodological challenges in terms of unifying the results of different studies that indeed used different methods (Cook 2008). Table 4.4 shows a summary of the minimal detectable changes (MDC; that is a cut-off point that does not necessarily represent clinical importance) for four different hop tests in the study of Reid et al. (2007) while Table 4.5 shows the clinimetric characteristics of patient-reported outcome measures (KOOS, K-SES and Lysholm). Although the wording of MDC looks close and similar to MCID, the former term implies the change of values that is not necessarily perceived clinically important for a patient or a clinician (Cook 2008). Based on the study of Reid et al. (2007, MCID was also assumed to be 5% for limb symmetry index (LSI) of single leg hop test. Appendix VI offers more details on the clinimetric qualities of patient-reported outcomes measures of function and objectively-measured indices of neuromuscular performance from which the thesis outcome measures were selected from on the basis of their reported clinimetric qualities.

Limb symmetry index	ICC (Lower 95%CI)	SEM (%) (upper 95% CI)	Error in individual's score (%)	Minimal detectable change (%)
Single-leg hop	0.92 (0.82)	±3.49(4.37)	±5.72	±8.09
6-m timed hop	0.82 (0.70)	±5.59 (7.01)	±9.17	±12.96
Triple hop	0.88 (0.80)	±4.32(5.41)	±7.08	±10.02
Cross over hop	0.84 (0.74)	±5.28(6.62)	±8.66	±12.25
combination of hop	0.93 (0.89)	±3.04(3.81)	±4.99	±7.05

Table 4.4: The minimal detectable change (MDC) for single leg hop (one of the primary outcomes of the trial of this chapter). Based on the study of Reid et al. (2007), a minimally clinical important difference (i.e. MCID) of 5% was noted between pre and post ACLR rehabilitation intervention (adapted from the study of Reid et al. 2007).

function measure	patients cohort evaluated	internal consistency	ICC	MDC	SEM	effect size	MCID
IKDC	knee injuries (ACL, meniscal, chondral)	0.77-0.91	0.90-0.95	8.8-15.6	3.2-5.6	2.11 at 12 months 0.76 at 6 month	6.3 at 6 months 16.7 at 12 months
	Cohort of mixed knee pathologies	0.92-0.97	0.87-0.99	6.7	2.4-4.6	1.13 at 6-28 months	11.5 at 6-28 months
KOOS	Knee injuries	pain= 0.84-0.91 symptom= 0.25-0.75 ADL=0.94-0.96 sport/rec=0.85-0.89 QoL=0.64-0.90	0.85-0.93 0.83.0.95 0.75-0.91 0.61-0.89 0.83-0.91	6.0-6.1 5.0-8.5 7.0-8.0 5.8-12.0 7.0-7.2	2.1 3.2 2.9 2.1 2.6	1.11 0.93 0.67 0.9 1.15	10 points
	Knee OA	pain=0.65-0.94 symptom=0.56-0.83 ADL=0.78-0.97 sport/rec=0.84-0.98 QoL=0.71-0.85	0.80-0.97 0.74-0.94 0.84-0.94 0.65-0.92 0.60-0.91	13.4 15.5 15.4 19.6 21.1	7.2-10.1 7.2-9.0 5.2-11.7 9.0-24.6 7.8-10.8	1.08 0.97 1.07 0.79 0.78	
Lysholm	knee injuries (ACL, meniscal, chondral)	0.65-0.73	0.88-0.97	8.9-10.1	3.2-3.6	1.01	
K-SES	ACL	daily activities=0.94 sport activities=0.91 knee functional activities=0.92 knee function in future =0.78					

Table 4.5: The clinimetric characteristics of patient-reported outcome measures. The minimal detectable changes for knee injuries that are associated with IKDC, KOOS (pain, symptoms, ADL, Sport/Recreation and QoL) and Lysholm were reported as 8.8-15.6, (6.0-6.1, 5.0-8.5, 7.0-8.0, 5.8-12.0, 7.0-7.2), 8.9-10.1, respectively. Adapted from Collin et al. (2011).

4.2.7 Primary objective outcome measure

Scoring of single leg hop test

For single leg hop to be considered successful, the participant's landing should be maintained for at least 2 seconds, therefore unsuccessful hops were repeated until deemed successful. All participants were instructed to start the test on the non-injured leg first. Distance was measured in centimetres from the toe at the start position to the heel at the landing position. Following two to three practice attempts, participants performed three maximal efforts, with the mean of the inter-trial replicates subsequently used for analysis. In addition to single leg hop test, the investigator had chosen to use the assessment of Limb Symmetry Index (LSI) for single leg hop test. The justification for using LSI in this trial was that the latter index is easy to use and quick to calculate. In addition, LSI involves the non-injured leg and utilise it as a reference point (within-subject between-leg comparisons) and of which the status of the injured leg can be determined based on the deficits calculated. It has been reported that an LSI more than or equal 85% represent normal knee function (Reid et al. 2007).

4.2.8 Primary subjective patient-reported outcome measures

Scoring of IKDC

IKDC form is scored from 0 to 100, with higher scores indicating better knee function and less symptoms, and lower scores indicating poorer knee function and more symptoms. It is worth mentioning that several studies have reported the use of the subjective knee section only (Higgins et al. 2007, Delcogliano et al. 2002). Because other sections of IKDC require other clinician's assessment, this study will therefore utilise the subjective knee section only.

Scoring of KOOS

The scoring of KOOS is based on 5 point Likert scale of 0 (no problem) to 4 (extreme problem). These score are then transformed to 0-100 scale (percentage score) with 0 indicating extreme knee problem while 100 indicating no knee problem. Test-retest reliability (ICC) of KOOS was reported for the sub-sections of pain, symptoms, ADL, Sport/Rec and QOL [0.83-0.93, 0.83-0.95, 0.75-0.91, 0.61-0.89 and 0.83-0.95, respectively] (Collins et al. 2011).

Scoring of Knee Self-Efficacy Scale (K-SES)

The K-SES form instrument consists of 22 items in four main domains using an 11-point Likert scale that range from 0 to 10. The scale of 10 demonstrates highest certainty about the ability to perform the task while 0 scale indicates the absence of certainty in the latter ability. The first three domains assess patient's perception toward current status in terms of physical activities (6 items), sports activities (5 items), daily activities (7 items) and knee function (4 items). The last domain assesses patient's perception in the ability to perform knee function in the future. The sum of item score is then calculated and divided by the total number of items (Brand and Nyland 2009).

Scoring of Lyhsolm

Lysholm knee rating scale has eight items with each individual items being scored in a different way; 1) limp [0,3,5], 2) support [0,2,5], 3) locking [0,2,6,10,15], 4) instability [0,5,10,15,20,25], 5)pain [0,5,10,15,20,25], 6) swelling [0,2,6,10], 7) stair climbing [[0,2,6,10] and 8) squatting [0,2,4,5]. Similar to the IKDC, the total score of 100 and is the sum of each response to the 8 items of Lyhsolm. The score of 0 represents poorest knee symptoms while higher scores indicating a higher level of function and less knee impairment. To view KOOS, IKDC, K-SES and Lysholm questionnaires, please see Appendix VII, VIII, IX, X, respectively.

4.2.9 Secondary objective outcome measures (neuromuscular performances)

Assessment of peak forces

After the patient's positioning on the isometric dynamometer, he/she completed a dynamometer-specific warm-up consisting of three sets of five replicates of 50% maximal voluntary muscle activation (MVMA) and one contraction of 70% and 90% of the participant's maximal capability to facilitate physiological potentiation for the assessment of peak force. After a verbal cue, an auditory signal was given randomly within 1-4 seconds and the participants attempted to activate their musculature as rapidly and forcefully as possible by attempting to extend or flex the knee joint as appropriate, against the immovable restraint (isometric) offered by the apparatus. Maximal effort was maintained for 3 seconds followed by another auditory signal that was given to the participant to cue neuromuscular relaxation. Intra-trial MVMA replicates were each separated by at least 10-seconds (Gleeson et al. 1996, Minshull et al. 2009). Commercially available software (Spike 2 software, version 5.16, Cambridge Electronics Design Ltd., UK) was used for all volitional data capture and interpretation. Volitional maximal peak force was recorded as the greatest response from each of the three intra-session replicates of maximal isometric muscle activations of the knee flexors. The peak forces of the knee extensors musculature was achieved in a similar manner.

Assessment of EMD

Electromyographic activity (EMG) was recorded from the m. biceps femoris during the estimation of volitional static flexion PF using bipolar rectangular surface electrodes (self-adhesive, Ag/AgCl; 10 mm diameter; Unilect, UK) that were applied longitudinally over the belly of the muscle parallel to the orientation of the muscle fibres. Similar EMG records were obtained from the m. vastus lateralis during the estimation of volitional static extension PF. The raw unfiltered EMG signals, which incorporated minimal intrusion from induced currents associated with external electrical and electromagnetic sources and noise inherent in the remainder of the recording instrumentation, were passed through a differential amplifier and were analogue-to-digitally converted at 2.5kHz sample rate, ensuring a significant margin of reserve between the highest frequency expected in the EMG signal and the Nyquist frequency (Gleeson et al. 2008).

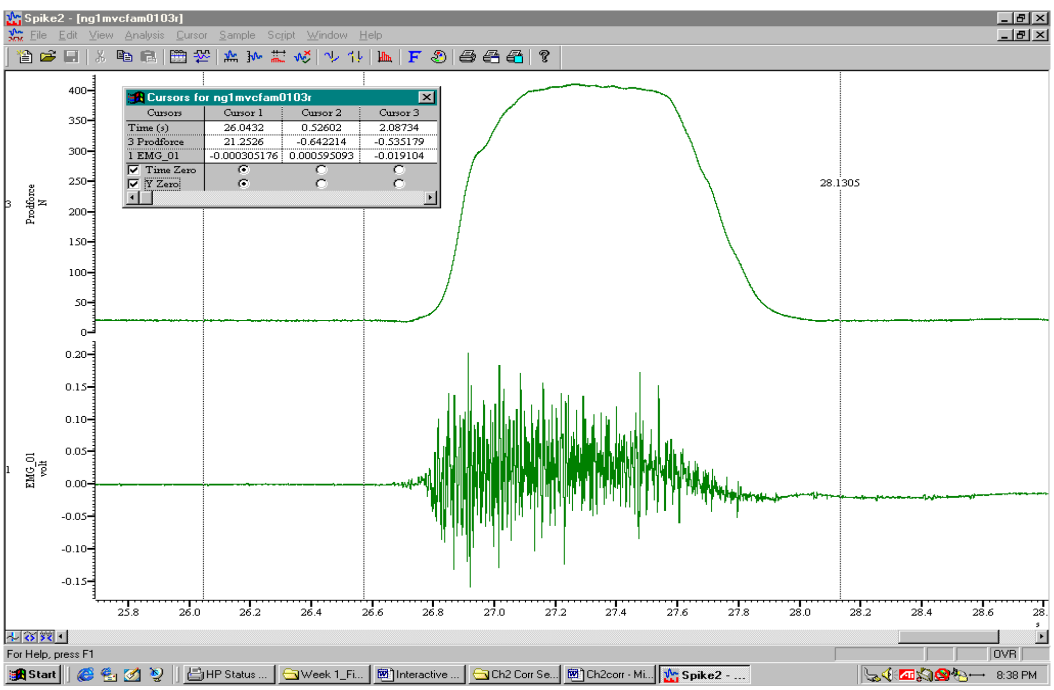


Figure 4.4: A time plot of force (upper trace) and electromyographic signal (lower trace) associated with one maximal voluntary muscle activation of the m. biceps femoris at 0.44 rad of knee flexion. The time

region between the first vertical cursor and the second is associated with a muscle being in a relaxed state prior to voluntary activation. The time region between the second vertical cursor and the third is associated with a muscle being activated voluntarily. The recorded EMG signal within this region will reflect both the physiological EMG ‘signal’ and the ‘noise’ inherent in the remainder of the recording system.

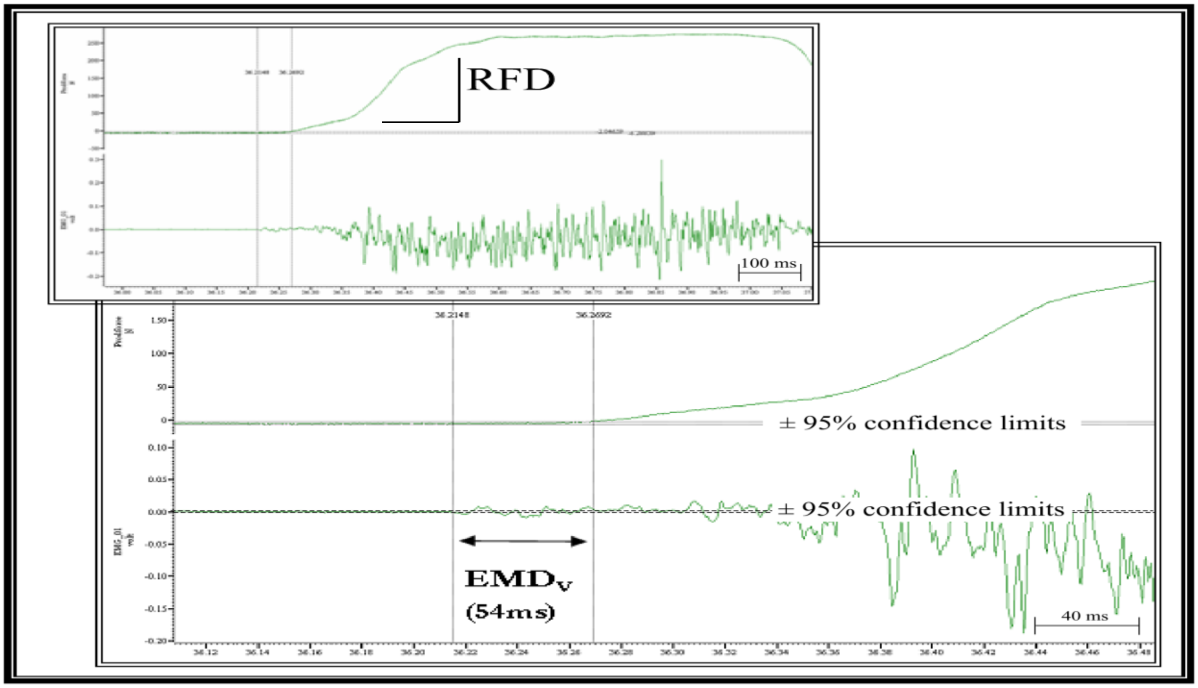


Figure 4.5: Example a magnified data of EMG (lower trace) associated with one maximal voluntary muscle activation (lower trace) to show representative calculation of volitional electromechanical delay (EMD), and above an example data to show representative calculation of rate of force development [RFD].

Assessment of rate of force development

Volitional RFD was calculated as the average rate of force increase between 25% and 75% of the volitional peak force (PF). Three intra-trial muscle activations were used to compute for the mean response of volitional RFD. Figure 4.5 offers an example of RFD with the vertical and horizontal lines representing the points of 25% and 75% of PF used for determining the RFD.

Assessment of anterior tibio-femoral displacement

Assessment of anterior tibio-femoral displacement (ATFD) was undertaken in the injured and contralateral (non-injured) legs for ACLR patients in the literature (Gleeson et al. 1992). The arthrometer system used in this assessment has been shown to be reliable and valid (Gleeson et al. 2005). The apparatus and patient orientation during the assessment is shown schematically in Figure 4.2. The knee joint was maintained at 25 degrees (0.44 radians) of flexion with foot positioning at 15 degrees (0.26 radians) of external rotation and 20 degrees (0.35 radians) of plantar flexion. Instrumentation to measure ATFD consisted of two linear inductive displacement transducers (DCT500C, RDP Electronics Ltd., Wolverhampton, U.K.: 0.025m range). The latter incorporated spring-loaded plungers that were adjusted accurately in three planes to provide perpendicular attachment to the patella and tibial tubercle. During measurements, both transducers were secured to the skin surface using tape and able to move freely only in the anterior-posterior plane relative to the supporting framework. The instrument monitored only the relative motion between the patella and tibial sensors and so facilitated the exclusion of measurement artefacts caused by extraneous movements of the leg during the application of anterior displacement forces. Anterior force was applied in the sagittal plane and in a perpendicular direction relative to the tibia by an instrumented force 142 handle incorporating a load cell (Model 31E500N0, RDP Electronics Ltd., Wolverhampton, U.K.: range 500N). This device was positioned behind the leg at a level 0.02m inferior to the tibial tubercle. The transducers were interfaced to a computerised data acquisition system (Cambridge Electronic Design Ltd., U.K.). Calibrated data from all transducers were sampled at 2.5 kHz.

Measurements on each knee were preceded by two practice trials. During each measurement, patients were instructed to relax the musculature of the involved limb. The latter was verified by inspection of on-line EMG records of the activity of m. biceps femoris and m. vastus lateralis. Rapid but gentle manual anterior-posterior drawer oscillations were used to facilitate relaxation and to establish a neutral tibio-femoral position from which all measurements were initiated. The same test administrator performed all measurements. Indices of ATFD were calculated as the mean of three intra-session replicates of the net displacement of the patella and tibial tubercle transducers at an anterior tibial displacement force of 160N applied in the sagittal plane, at a rate of 67 ± 7 N·s^{-1}, and was tolerated well by symptomatic patients (Gleeson et al. 1992, Gleeson et al. 2008).

Assessment of objective sensorimotor performance (SMP)

Sensorimotor performance (SMP) is defined as the ability of a person to scale volitional force precisely (Gillian 2009). The SMP task is a slow, self-regulated muscular activation (at a rate of ~200 $N{\cdot}s^{-1}$]), which attempts to mimic the process of muscle re-education following disruption to the neuromuscular system during injury or surgical intervention. This type of activation utilises feedback from pre-learned strategies of joint protection. Based on this fact, SMP is assessed when the involved musculature is activated to meet or equal a given percentage of volitional peak force (PF) in a blinded fashion. An error (force error) in reproducing this given force following a standardised delay is then expressed as SMP (Gleeson et al. 2008). Force error (FE) derived from a SMP task that required the 'blinded' attainment of a target force using the knee flexors/extensors, was evaluated. The target force was set at 50% of PF and at 30º knee flexion to reflect what is considered to contribute to peak power outputs from functional neuromuscular performance based on expected power-velocity and force-velocity relationships. The extent of FE indicates the constant error or bias or around a target force meaning that lower scores describe better SMP.

Experimentally, each assessment included a familiarisation session, whereby participants were blindly familiarised with 50% of their daily peak force. This familiarisation process is consistent with recommendations that sub-maximal isometric performances should be based on a relative level within the same day due to normal biological variation (Gleeson et al. 2008). The familiarisation involved participants undertaking a standardised series of practices using the involved musculature (knee quadriceps/hamstrings) with the aim of matching the target force (50% peak force) as closely as possible, while minimising any subsequent learning effects during assessments. During familiarisation practice, participants received only standardised verbal feedback from the assessor in order to improve performance precision. This was achieved by blinding participants to both the absolute level of the prescribed target force and the scale of measurement used to offer feedback (Lauzière et al. 2012).

Verbal feedback from the assessor was withdrawn progressively as the participants familiarised themselves to the requirements of the task. Of 10 practice trials, the task was considered to have been learned if the participant was consistently able to produce seven or more values demonstrating errors within 2.0 N of the blind target force (99% confidence limits of the technical error associated with the load cell system). Reproducing the target force was indicated when the participant achieved full relaxation of the involved knee flexor/extensor muscles (Gleeson et al. 2008). To evaluate the participants' capacity on SMP performance, FE was calculated as the percentage difference between the verbally requested by the assessor for the force generating tasks and that produced on the dynamometer. For example, in the force perception task, if the verbally requested score was 45 % and the actual force produced on the dynamometer was 50 %, the absolute error was 5 % (Lauzière et al. 2012). For any given performance trial, FE was computed using the generic formula: FE = (observed performance value – target performance value) / target performance value) × 100%). The mean error of the ten trials was used for subsequent data analysis (Gleeson et al. 2008).

4.2.10 Orthopaedic-related factors influencing the main outcomes of knee performance

Waiting time for surgery

The consequences of patients having lengthy wait for surgery have received little attention in the literature. However, wait time to surgery has been deemed as an essential factor for determining successful surgical outcomes (Braybrooke et al. 2007, Derret et al. 1999). In a cross sectional study, Derret et al. (1999) had used Short-Form 36 (SF-36) health-related questionnaire to assess the influence of waiting time tor surgery on patient’s quality of life and symptoms in a group of patients who were waiting for prostatectomy, knee and hip joint replacement surgeries. The latter study reported that patients with severe symptoms had significantly more desire for surgery than those with fewer symptoms. Although no worsening of symptoms was reportedly associated with increasing wait time to surgery, the authors attributed this lack of association due to the design of the study as during the waiting time the cross sectional study could not assess the change to increased acceptance of poor health as well as the design of SF-36 showing inability to address some elements of health status related to certain medical conditions (e.g. relevant health status of men waiting for prostatectomy). Braybrooke et al. (2007) had also used SF-36 to investigate the effect of wait time to surgery on patients waiting for lumbar spinal surgery. The latter authors had reported that following surgery, less improvement in the surgical outcomes were associated with longer waiting time for surgery. In addition, using patient-derived functional outcome measure, a negative relationship was found between prolonged wait to surgery and optimal outcomes following posterior lumbar spinal surgery for degenerative conditions.

Unstructured physical activity

The energy output as a result of physical exercise or activity can be categorised into two main forms: the planned and recurring exercise which is commonly termed as “structured physical activity” (e.g. well-planned physical-therapy sessions in the hospital) and the habitual, ordinary and leisure time physical activities (commonly known as "unstructured physical activity") such as walking. In the context of this chapter, unstructured physical activity is the unsupervised activity that takes place away from the hospital-based setting. There are very few studies which measured unstructured physical activities at home environment following ACLR surgery. Ageberg et al. (2012) investigated the association of leisure time physical activity and risk for knee and hip replacement. A significant correlation (0.66) was observed between the latters indicating that reduced risk of knee or hip replacement is associated with those demonstrating high leisure time physical activities. In the context of the current study, the influence of the unstructured physical activity endorsed by patients at their home-based environment is an important factor that can shape up the speed and extent of recovery following ACLR surgery. Of the most commonly used questionnaires to record unstructured physical activities is the 7-Day Physical Activity Recall Questionnaire. The latter questionnaire had been reported to be both reliable and valid (Soundy et al. 2007). Therefore the trial of this chapter will utilise the latter questionnaire in order to quantify the level of physical activities patients are engaged in away from the prescribed well-planned programme in the hospital setting.

Body mass

Holla et al. (2013) had reported in their study that body mass index (BMI) and depressed mood had been independently associated with limitation of activity and knee pain (assessed by both self-reported questionnaire and performance based activities). The latter study revealed that BMI, in particular, was a major contributor for variances found in performance-based and self-reported activities of the knee. In another study Elbaz et al. (2011) found that BMI was one of the main factors that contributed to causing knee osteoarthritis (OA) and showed significant correlation between BMI and worst symptoms reported using Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and Master Universities Osteoarthritis Index (WOMAC) questionnaires (p=0.009 and p=.001, respectively).

4.2.11 Recording structured, unstructured physical activities and patient's compliance

Determining the frequency, intensity and duration of exercises during rehabilitation is an important factor for controlling the heterogeneity of exercise dosage. Because ACLR rehabilitation endorses different exercises for knee flexors and extensors, recording the FIT associated with "structured physical activities" can offer an appropriate description of how much exercise the patients had actually done the exercises across the entire rehabilitation programme. The study of Heijne and Werner (2007) had involved the calculation of training volume by recording the number of sets, repetitions and resistance for each exercise taken in one rehabilitative session. The latter authors had consequently been able to determine the effects of two types of exercises (quadriceps and hamstrings) introduced in weeks 4 and 8 following ACLR surgery.

The precise dosing of “structured physical activity” in this trial was done by the investigator using a log diary in which time spent, sets, repetitions and resistance (weight) lifted in each exercise was recorded throughout the assessment period. On the other hand, the “unstructured physical activity” is concerned with the assessment of patient’s physical activity that took place in their home- and leisure-based environment. The latter was assessed using the self-reported questionnaire “7 day physical activity recall”. Patients were asked to fill in the latter questionnaire during each test occasion in which their unstructured physical activities of the last week would be documented. This had allowed the investigator to get an estimate of the amount of unstructured physical activities carried out in the past weeks prior to patient’s test occasion. The total amount of work done during each rehabilitative session (structured physical activity) was computed by obtaining the quantified FIT of exercises which was then converted into Kilocalories/day. Similarly, the amount of unstructured physical activities recoded in the 7 day physical activity recall was converted into Kilocalories/day. For a detailed overview on the steps of conversion into Kcal/day, please refer to Appendix XI for structured physical activity and Appendix XII for unstructured physical activity. Moreover, patient’s compliance to ACLR rehabilitation was assessed by filling in a logbook diary in which the number of rehabilitation visits attended was recorded. The total duration of physiotherapy session (structured physical activity) in both groups during the entire rehabilitation period was same (an average of 30 minutes per session).

4.2.12 Verification of successful experimental manipulation of treatment.

The investigator of this trial had verified that accelerated rehabilitation had achieved earlier isometric quadriceps exercises, leg curl, seated leg press, OKC for quadriceps and full ROM weight bearing. This was achieved in coordination with the research physiotherapy staff who kept a log book to confirm achieving the latter activities in both the accelerated and contemporary rehabilitation groups.

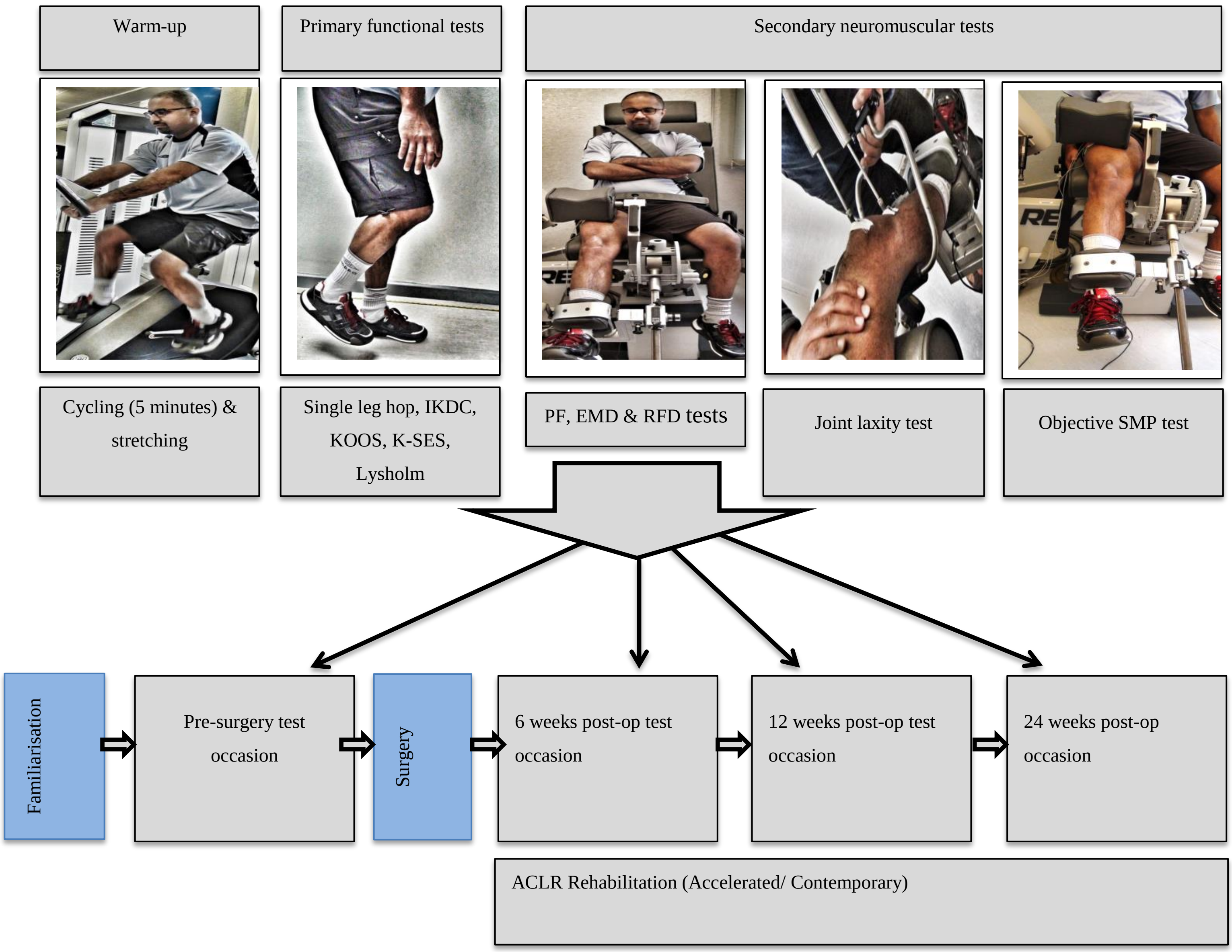


Figure 4.6 The experimental design illustrating the test occasions and protocol of the trial (effects of accelerated rehabilitation following ACLR rehabilitation).

Keys:

EMD: electromechanical delay. RFD: rate of force development. PF: peak force. SMP: sensorimotor performance.

4.2.13 Statistical analyses

The software that was utilised for the statistical analysis of this trial was the Statistical Package for Social Sciences (SPSS; v. 20.0). The clinical efficacy of accelerated rehabilitation conditioning was assessed using separate analyses of variance (ANOVAs) for the primary objective functional (single leg hop test) primary patient-reported measures (IKDC, KOOS, K-SES, Lysholm), and the secondary objective neuromuscular measures of anterior tibio-femoral displacement (ATFD), peak force (PF), electromechanical delay (EMD), rate of force development (RFD), sensorimotor performance (SMP).

The ANOVA model involving factors of group (accelerated; contemporary) by leg (non- injured/injured) by test occasion [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery] with repeated measures on the latter two factors was used to test the null-hypothesis of no statistical interaction between the mean group responses of patients undertaking accelerated and contemporary rehabilitation conditioning over time for outcomes that had assessed the performance of each leg separately. The outcome performances associated with the knee hamstrings and quadriceps of both injured and non-injured legs were assessed separately, where appropriate. An ANOVA model using factors of group (accelerated; contemporary) by test occasion (pre-surgery, 6,12 and 24 weeks post-surgery) with repeated measures on the latter factor was used to test the equivalent null-hypothesis for outcomes in which the assessment of separate leg performance had not been required (IKDC, KOOS, Lysholm and K-SES questionnaires).

In addition, an analysis of covariance (ANCOVA) was used to assess the effects of anthropometric and orthopaedic-related factors on the clinical efficacy on primary outcomes measures (single leg hop and IKDC) and patient-reported outcome measures (KOOS, K-SES and Lysholm) for accelerated and contemporary rehabilitation programmes by controlling age, height, body mass, waiting time and unstructured physical activity. The ANCOVA model involving factors of group (accelerated; contemporary) by test occasions [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery] with repeated measures on the latter factors was employed to test null-hypothesis for outcomes between the group mean responses for the patients in the both groups following ACLR rehabilitation programmes. Moreover, relative effect size (Cohen's *d)* was calculated using pooled standard deviations (SD) for each study ([post-test mean control–post-mean experimental] ÷ pooled SD). By utilising the difference between the post-test means, the relative effect size was calculated using standard deviation units in the denominator [also known as standardized mean difference] (Durlak 2009).

4.2.14 Power of the study

A *priori* alpha level was set at $p<0.05$. The experimental design offered an approximate 0.80 power of avoiding type 2 error when employing at least a detectable difference (a minimum extent of difference between the effects of experimental interventions (accelerated versus contemporary) that might be considered clinically and biologically meaningful in primary outcomes [single leg hop] (Sport Science 2006). The sample size is also justified based on previous studies. In the study of Gleeson et al. 2008, the experimental design had offered an approximate 0.80 power of avoiding a Type II error when employing a least detectable difference of 0.2 mm, 16 N, 4ms and 0.3 units during comparisons of ATFD, PF, EMD, and IKDC scores, respectively. Therefore, based on the latter least detectable difference (MCD), an internet-based sample size calculator that has been scientifically verified (Glazier et al. 2010) was used to estimate sample size of this study. It was estimated that 50 participants will be needed [accelerated group (n=25); contemporary group (n=25)] for appropriate experimental design sensitivity and statistical power involving random-allocation to experimental or control groups. Where selected assumptions underpinning analysis of variance had not been met, Greenhouse-Geisser (GG) adjustments of the degrees of freedom associated with the experimental and error variances were used.

4.2.15 Checking the normality of data

Normality of data in this trial was evaluated using Shapiro-Wilks (numerical test) and Q-Q plot (graphical test). These tests are designed for small to moderate sample sizes and have good power across a range of non-normal distribution. A variable of interest of more than 0.05 of p value for the null hypothesis of Shapiro-Wilk test (i.e. the population is normally distributed) was deemed normally distributed (i.e. there is no difference between the data examined and the normally distributed population). The patients in the accelerated and contemporary groups showed similarities at baseline on neuromuscular performance and patient-reported outcome measures. Accordingly this allows the investigator of this trial to use parametric tests.

4.2.16 Ethical approval

This study met the ethical standards suggested by Harriss and Atkinson (2011), and the study was approved by the Ethics Committee of the Shropshire area NHS Ethics Committee [REC reference 11/WM/0417 (Appendix III)] and had received scientific merit approval from the Research Committee of

Robert Jones and Agnes Hunt Orthopaedic and District Hospital Foundation NHS Trust, UK (Appendix IV).

4.2.17 Data protection

A 'master copy' of individual identification numbers unique to each participant was stored in a safe place on site and was accessible only to the named key researcher. This identification number corresponded with the participant's personal details and any participant information material and consent forms. This number was used throughout the research of the study to correspond with any scientific data collected, no personal and identifying information were used. All data was collected by chief researcher throughout the clinical trial and access to data was only to the key researchers and associated collaborators.

All collated data was stored electronically on the designated research laptop's hard drive and back-up disc. The laptop and back-up discs were password protected, including the master copy of participants identification numbers (stored in a separate secure location within the physiotherapy clinic). Any published literature of this clinical trial did not include any names other than basic demographic data e.g. subject's number, age, sex, height etc. Written documentation and data were also stored in a paper format in the participant's medical notes as per normal clinical practice.

The storage and subsequent destruction of data are compliant with the Data Protection Act 1998. Written documentation and data have been stored in a paper format in the participant's medical notes as per normal clinical practice. These will be destroyed after 8 years following discharge as per the health care records policy at RJAH. All forms of data were securely kept in locked cabinets within locked rooms. Only the principal researchers and associated collaborators had the permission to use and access. All collected information during the course of this research was kept strictly confidential and any information that could leave the hospital had patient's name and addresses removed to ensure anonymity.

4.2.18 Indemnity

Queen Margaret University, Edinburgh was the academic sponsor for this PhD research progrramme and has taken full responsibility and indemnity cover (Confirmation of Insurance, Marsh Ltd, Queen Margaret University, Edinburgh and Subsidiary Companies; Insurer: RSA, Insurance Certificate RTT153481, Public Liability 20M) for any harm that might come to participants as a result of the research design and management of each day. Similarly, Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS foundation have given the responsibility for issues arising from the conduct of this research including the supervision of PhD candidates and any harm that might have while they are working with the patients in the mentioned hospital. Additionally, the latter hospital has taken the responsibility for the patients' welfare in all other aspects of their routine care.

4.3 Results

4.3.1 Changes in single leg hop (objective functional measure)

A factorial analysis of variance (ANOVA) using factors of group (accelerated; contemporary) by test occasion [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery] by leg (injured; non-injured) with repeated measures on the latter two factors revealed there was no significant interaction for change scores [pre-surgery (0 weeks) to 12 and 12 to 24 weeks post-surgery] of single-leg hop test [$F_{(1,38)\ GG}$=0.8; ns] (Figure 4.7). As no interaction was found using three way interactions, a two way factors (group by test occasions) to investigate the influence of injured and non-injured leg over time, revealed no significant interactions between the two groups over time at pre-surgery (0 weeks) to 12, and 12 to 24 weeks post-surgery, suggesting that the single leg hop performance of injured and non-injured legs over time were not different.

Anthropometric and orthopaedic-related factors [age, height, body mass, visits to physiotherapy sessions, waiting time to surgery and unstructured physical activities (home and leisure-based exercises)] were also statistically assessed to see whether they affected between-subject variability. As a result the latter factors were utilised in the statistical model. The justification for using these variables had been mentioned earlier in the method of this chapter. An analysis of covariance (ANCOVA) test revealed significant interactions (approaching a significant value of 0.05) of group by leg by time with repeated measures on the latter two factors for the change scores of single leg hop using the candidate covariates of body mass ($F_{(1.9,72.4)\ GG}$=2.7; p=0.07), unstructured physical activity ($F_{(1.9,\ 72.6)\ GG}$= 2.8; p=0.06) and waiting time ($F_{(1.9,\ 71.8)\ GG}$= 2.9; p=0.05). The results suggested that the patients in the accelerated and contemporary groups showed different patterns of improvement for single leg hop performance over time in the injured and uninjured legs. Group mean scores for single leg hop suggested that while patients in both the accelerated and contemporary groups showed improved performance during the follow-up period, group mean scores associated with the accelerated rehabilitation conditioning confirmed superior capability for both legs but that this was more pronounced in the injured leg ($F_{(1.9,\ 73.8)\ GG}$= 3.8; p=0.02). A *priori* 'interaction' testing of greater change scores in single-leg hop associated with the accelerated versus contemporary rehabilitation suggested that superior performance for the injured leg at 12 weeks post-surgery compared to pre-surgery when controlling for body mass ($F_{(1,\ 37)\ GG}$=3.7; p=0.04), unstructured physical activity ($F_{(1,37)\ GG}$= 4.1; p=0.03) and waiting time ($F_{(1,37)\ GG}$= 2.7; p=0.04). The latter contributed most to the overall significant interaction for the injured leg of patients in accelerated and control groups.

The relative effect size for group mean change scores of single-leg hop (injured leg) suggested that accelerated group showed moderately more improved performance than contemporary group at pre-surgery (0 weeks) to12 weeks post-surgery (*d*=0.21 for injured leg). In general, the group mean peak relative difference (%) in improvement of patients' single leg hop function associated with accelerated versus contemporary conditioning at 12-24 weeks was 1% for the injured leg.

Limb Symmetry Index (LSI) have been reported in the literature as being one of the most stringent criteria for allowing patients with ACLR to return to vigorous physical activities (Reid et al. 2007). The absolute scores for LSI of single leg hop revealed no statistically significant interaction between accelerated and contemporary group in the factorial repeated measures ANOVA analysis ($F_{(1.9,\ 73.0)\ GG}$ =2.1; ns) using factors of group by time by leg. Similarly no superiority was found in the accelerated group over the contemporary group in a priori "interaction" testing for change scores of LSI for single leg hop performance between pre-surgery (0 weeks) to 12 weeks post-surgery ($F_{(1,\ 38)\ GG}$ =2.0; ns) and between the change scores of 12 to 24 weeks post-surgery ($F_{(1,\ 38)\ GG}$=2.4; ns). However both the accelerated and contemporary groups had achieved more than 85% of LSI single leg hop scores at 12 weeks post-surgery, a percentage required in the criteria for returning to sporting and vigorous activities following ACLR surgery (De Carlo and McDivitt 2006), with mean scores of 110.8 % and 113.5 at 12 weeks and 112.7 and 113.8 at 24 weeks post-surgery for LSI of single leg hop in the accelerated and contemporary groups, respectively.

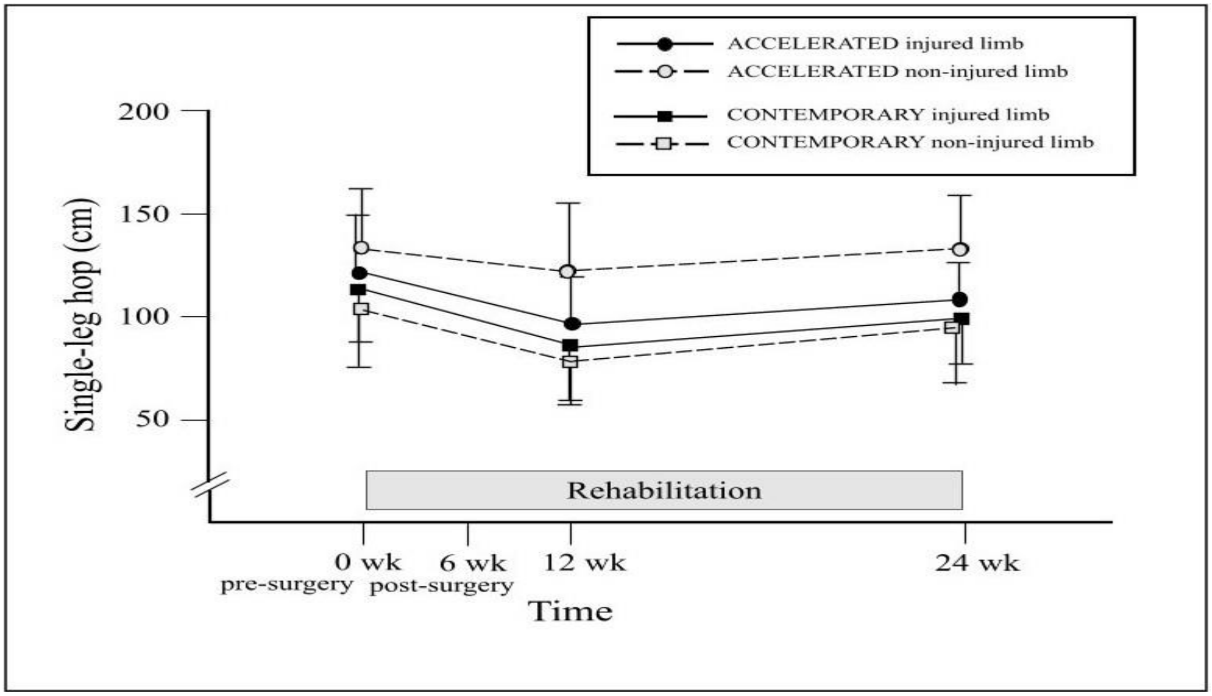


Figure 4.7: Single leg hop scores of accelerated and contemporary groups for both the injured and non-injured legs from pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery during ACLR rehabilitation.

4.3.2 Changes in subjective functional measures

IKDC, K-SES and Lysholm

An ANOVA with repeated measures showed no significant group (accelerated; contemporary) by test occasion [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery] interaction elicited from the change scores of patient-reported outcome scores of IKDC at pre-surgery (0 weeks)-12 and 12-24 weeks post-surgery ($F_{(2.5,\ 95.7)\ GG}$=0.5; ns) and ($F_{(2.3,94.3)\ GG}$=0.7; ns), respectively, indicating that accelerated conditioning had not adversely affected the outcomes of perceived knee function. Moreover, when adjusting for anthropometric and orthopaedic-related factors, no superiority of accelerated group over contemporary group was found in change scores during any follow up periods following ACLR surgery ($F_{(1,\ 38)\ GG}$ =1.4; ns) using ANCOVA for group by time by leg factors.

Analysis of variance with repeated measures showed no significant group (accelerated; contemporary) by test occasion [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery] interaction elicited from the change scores of patient- reported outcomes of Lysholm ($F_{(2.6,\ 101)\ GG}$= 44.1; ns), and K-SES [daily activity] ($F_{(2.5,\ 96.5)\ GG}$=0.1; ns), K-SES [physical activity] ($F_{(2.6,\ 101.3)\ GG}$=1.0; ns), K-SES [sports activity] ($F_{(2.5,\ 95.1)\ GG}$=0.7; ns) and K-SES [function in future] ($F_{(2.4,\ 94.6)\ GG}$=0.5; ns). Moreover, using the covariances of body mass, unstructured physical activity and waiting time, no superiority of accelerated group over contemporary group in K-SES and Lysholm change scores associated with the accelerated versus contemporary rehabilitation was suggested during any follow up periods following ACLR surgery. The latter findings suggested that accelerated conditioning had not adversely affected the outcomes of perceived knee function

KOOS

As previously mentioned the sub-sections of KOOS should be treated as separate scores. An ANOVA using factors of group by test occasion with repeated measures on the latter factor showed that while patients in both experimental and contemporary groups improved the change scores of KOOS in pain sub-section (KOOS[P], function (KOOS [F], sports and recreation (KOOS[SR] and quality of life (KOOS [QOL] during the follow-up period, group mean change scores associated with the accelerated rehabilitation group were superior than the contemporary group (*p* value less or approaching 0.05) in KOOS [P] ($F_{(2.4,92.7)\ GG}$=2.3; *p*=0.08) and KOOS [QOL] ($F_{(2.4,\ 92.8)\ GG}$= 2.9; *p*= 0.04). The results suggested that the patients in the accelerated and contemporary groups showed different patterns of improvement for KOOS (pain and quality of life) over time. Group mean scores for KOOS (pain and quality of life) suggested that while patients in both the accelerated and contemporary groups showed improved change scores during the follow-up period, group mean change scores associated with the accelerated rehabilitation conditioning confirmed superiority ($F_{(2.4,\ 92.4)\ GG}$= 3.8; p=0.02). A *priori* ‘interaction’ testing of greater change scores in KOOS (pain and quality of life) associated with the accelerated versus contemporary rehabilitation suggested that superior change scores at 12 weeks post-surgery compared to pre-surgery KOOS [P] ($F_{(1,\ 38)\ GG}$= 2.4; p=0.03) and KOOS [QOL] ($F_{(1,\ 38)\ GG}$= 3..4; p=0.02 , contributed most to the overall significant interaction in the accelerated and control groups

The relative effect size for group mean change scores of suggested that accelerated group showed moderately more improved change scores than contemporary group at pre-surgery (0 weeks) to12 weeks post-surgery for KOOS [P] and KOOS [QOL] scores (*d* = 0.63, 0.5, respectively) between pre-surgery (0) to 12 weeks post-surgery. The corresponding group mean scores at pre-surgery (0) to 12 weeks post-surgery of patients undertaking accelerated rehabilitation conditioning showed a 50% % and 19% advantages of KOOS [P] and KOOS [QOL], respectively, in the accelerated group over the contemporary group.

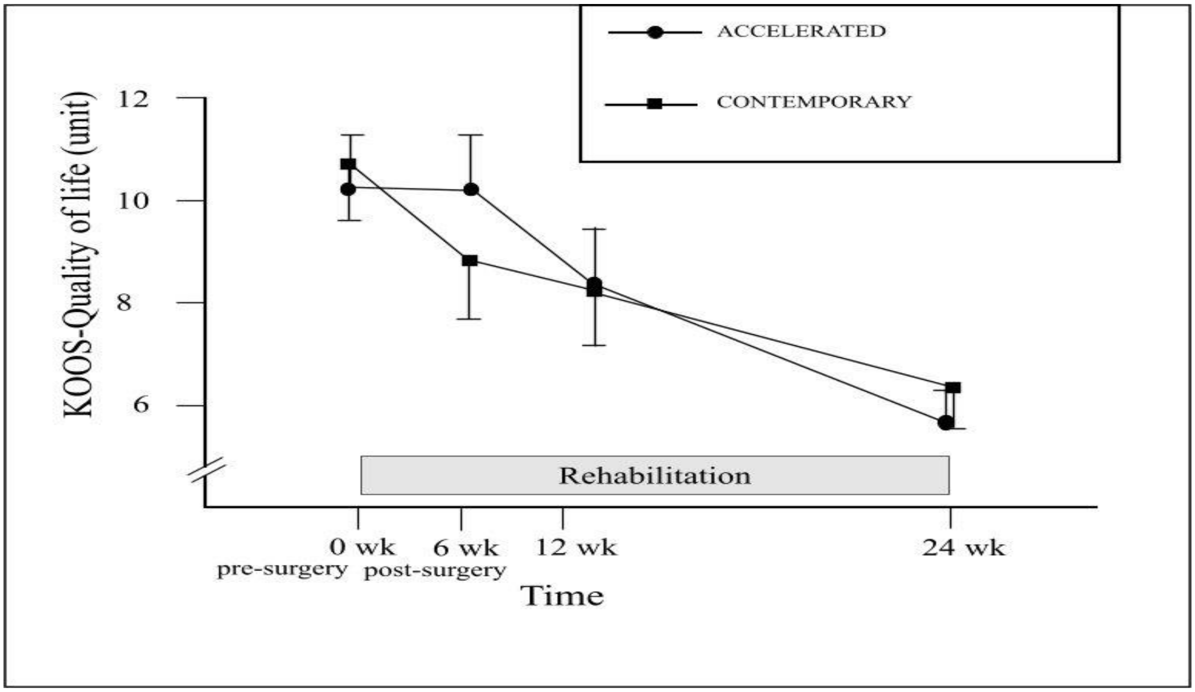


Figure 4.8: Mean KOOS (Quality of Life) scores of accelerated and contemporary groups over time [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery].

4.3.3 Objective neuromuscular measures:

Peak forces (PF) for quadriceps and hamstring musculature

Factorial ANOVA showed no significant group (accelerated; contemporary) by leg (non-injured; injured) by test occasion [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery] interaction with repeated measures on the latter two factors elicited from change scores of the peak force for quadriceps and hamstrings at pre-surgery (0 weeks)-12 and 12- 24 weeks post-surgery ($F_{(1.7,\ 65.3)\ GG}$=0.1; ns) and ($F_{(2.3,\ 90.4)\ GG}$= 1.0; ns), respectively. This pattern of non-significant interaction was also observed on two way factors (group by test occasion), indicating that the peak forces of hamstrings and quadriceps of the injured and non-injured legs had not been differentially influenced over time by the accelerated conditioning. However, an ANCOVA test using group by leg by test occasion with repeated measures on the latter two factors showed a statistically significant interaction in the change scores of peak force for hamstrings musculature was observed (approaching a significant value of 0.05) when adjusting for body mass ($F_{(1,37)\ GG}$=6.3; p=0.01), unstructured physical activity ($F_{(1,37)\ GG}$=6.2 ; p=0.01) and waiting time ($F_{(1,37)\ GG}$=6.4; p=0.01). The results suggested that the patients in the accelerated and contemporary groups showed different patterns of improvement for peak force for hamstrings musculature over time in the injured and uninjured legs. Group mean scores for peak force of hamstrings suggested that while patients in both accelerated and contemporary groups showed improved performance during the follow-up period, group mean scores associated with the accelerated rehabilitation conditioning confirmed superior capability for both legs but that this was more pronounced in the injured leg ($F_{(1,\ 37.8)\ GG}= 4.2$; $p=0.02$). A *priori* 'interaction' testing of greater change scores in single-leg hop associated with the accelerated versus contemporary rehabilitation suggested that superior performance for the injured leg at 12 weeks post-surgery compared to pre-surgery when controlling for body mass ($F_{(1.37)\ GG}=3.2$; $p=0.01$), unstructured physical activity ($F_{(1,\ 37)\ GG}=2.9$; $p=0.04$) and waiting time ($F_{(1.37)\ GG}=3.4$; $p=0.02$). The latter contributed most to the overall significant interaction for the injured leg of patients in accelerated and control groups.

Table 4.6: Percentage changes (injured legs) in the functional (single leg hop and patient-reported measures) and objective neuromuscular measures between pre-surgery (0 weeks) to 12 and 12 to 24 weeks post-surgery.

		pre-12 week	12-24 week
		%	%
Single leg hop	accelerated	12	11
	contemporary	10	10
LSI (hop)	accelerated	74	88
	contemporary	63	69
ATFD (laxity)	accelerated	62	76
	contemporary	70	82
PF quads	accelerated	18	2
	contemporary	18	2
PF hams	accelerated	16	8
	contemporary	12	4
EMD quads	accelerated	9	6
	contemporary	13	1
EMD hams	accelerated	22	14
	contemporary	21	8
RFD quads	accelerated	13	13
	contemporary	0	1
RFD hams	accelerated	45	27
	contemporary	11	11
SMP quads	accelerated	0	46
	contemporary	29	28
SMP hams	accelerated	2	35
	contemporary	18	33
Lysholm	accelerated	22	27
	contemporary	28	32
IKDC	accelerated	15	36
	contemporary	18	27
KOOS (P)	accelerated	106	212
	contemporary	56	140
KOOS (QOL)	accelerated	44	43
	contemporary	25	36
K-SES (mean of four domains)	accelerated	54	46
	contemporary	21	35

Keywords: KOOS (P): pain, KOOS (QOL): quality of life, K-SES, K-SES (PA): physical activity.

The relative effect size at pre-surgery (0 weeks) to 12 weeks post-surgery for hamstrings peak force (injured leg) revealed that group mean change scores showed better improvement effect in the accelerated than contemporary groups (0.6, 0.3; injured legs, respectively), corresponding to 4 % advantage for the accelerated over the contemporary group in the injured leg.

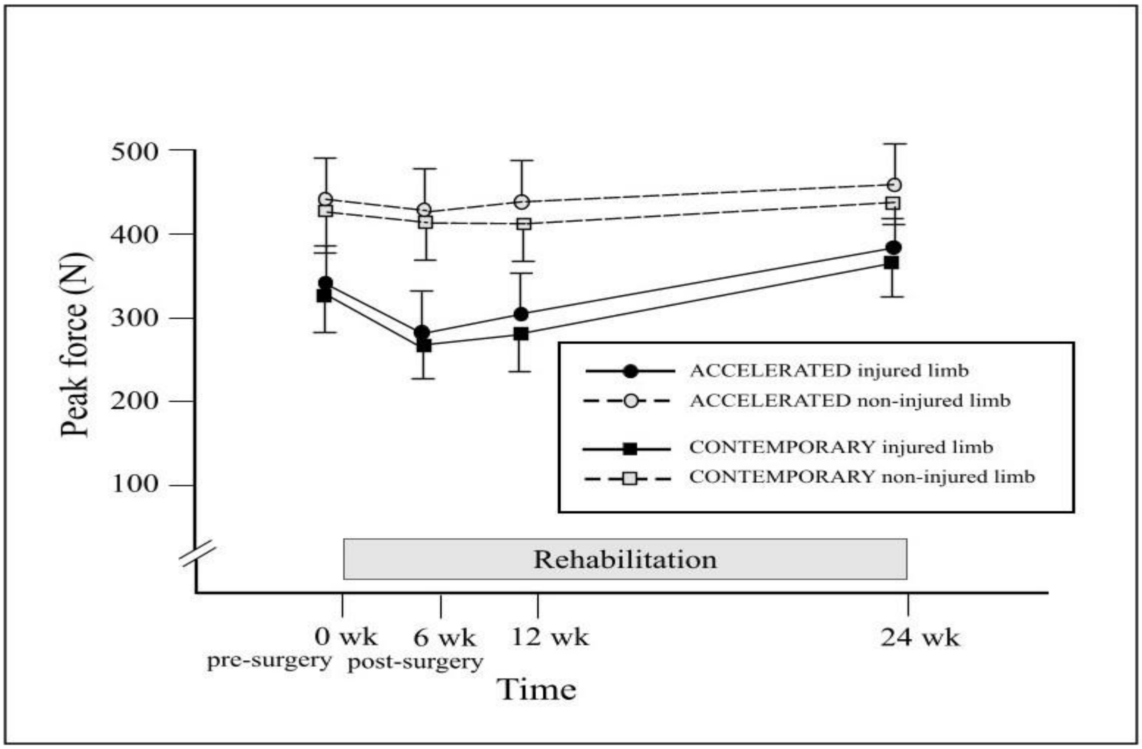


Figure 4.9: Measurement of quadriceps peak force (N·s-[1]) of accelerated and contemporary groups for the injured and non-injured legs from pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery.

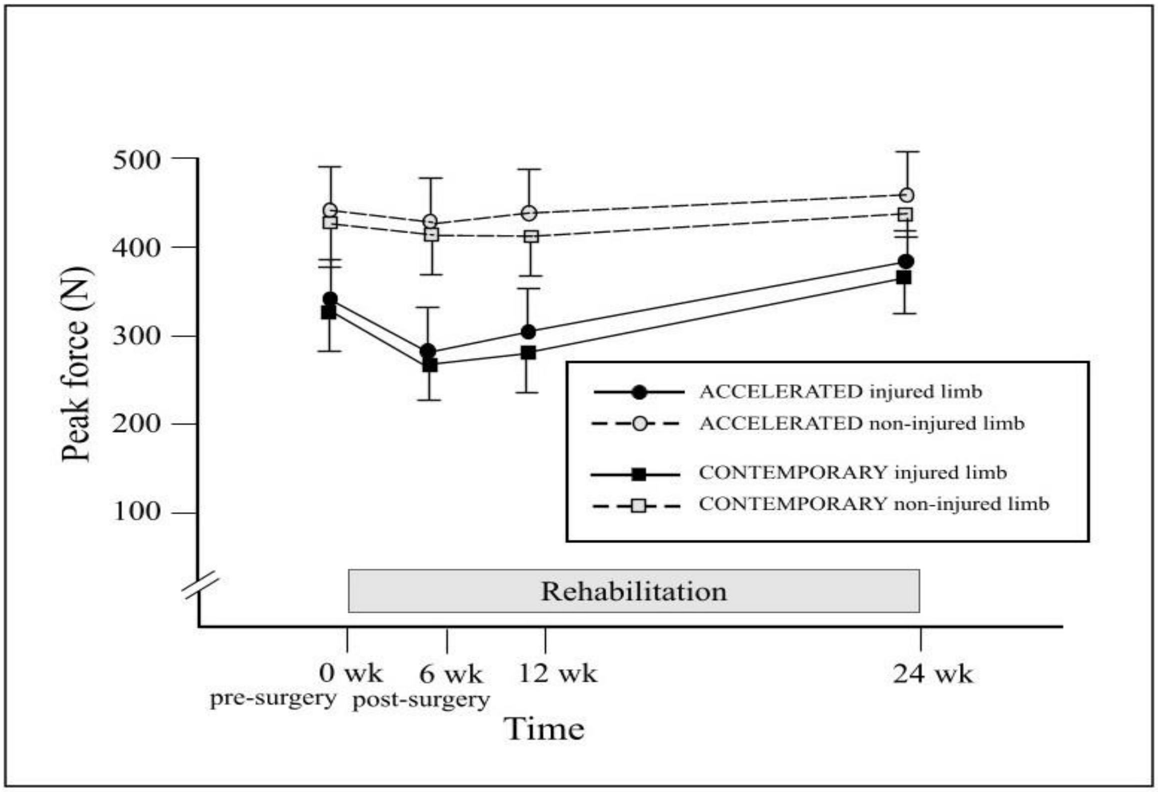


Figure 4.10: Measurement of hamstrings peak force ($N \cdot s^{-1}$) of accelerated and contemporary groups for the injured and non-injured legs from pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery.

Rate of force development (RFD) for quadriceps and hamstrings

No significant interaction was elicited from the change scores of RFD for quadriceps and hamstrings musculature ($F_{(2.5,\ 97.8)\ GG}$=0.4; ns) and ($F_{(2.5,\ 97.3)GG}$=1.4; ns), respectively, when using factorial ANOVA with repeated measures (group by leg by test occasion). This pattern of non-significant interaction in change scores of RFD for quadriceps and hamstrings was also observed on two way factors (group by test occasion), indicating that the RFD of hamstrings and quadriceps of the injured and non-injured legs had not been differentially influenced over time by the accelerated conditioning. However, when controlling for orthopaedic-related factors (body mass, unstructured physical activity and waiting time), significant interaction (group by leg by test occasion) in change scores of hamstrings RFD (approaching a significant value of 0.05) for body mass ($F_{(1,37)\ GG}$= 3.7; p=0.06), waiting time ($F_{(1,37)\ GG}$= 3.0; p=0.08) and unstructured physical activity ($F_{(1,37)\ GG}$= 3.6; p=0.06) was observed. The results suggested that the patients in the accelerated and contemporary groups showed different patterns of improvement for in change scores of hamstrings RFD over time in the injured and uninjured legs. Group mean scores for peak force of hamstrings suggested that while patients in both accelerated and contemporary groups showed improved performance during the follow-up period, group mean scores associated with the accelerated rehabilitation conditioning confirmed superior capability for both legs but that this was more pronounced in the injured leg ($F_{(1,\ 37.8)\ GG}$= 3.2; p=0.02). A *priori* 'interaction' testing of greater change scores in single-leg hop associated with the accelerated versus contemporary rehabilitation suggested that superior performance for the injured leg at 12 weeks post-surgery compared to pre-surgery when controlling for body mass ($F_{(1,37)\ GG}$= 3.9; p=0.02), unstructured physical activity ($F_{(1,37)\ GG}$= 4.5; p=0.04) and waiting time ($F_{(1,37)\ GG}$= 4.1; p=0.04). The latter contributed most to the overall significant interaction for the injured leg of patients in accelerated and control groups. The relative effect size at pre-surgery to 12 weeks post-surgery for hamstrings RFD (injured leg) revealed that group mean change scores showed moderate improvement effect (*d*=0.5 injured legs) in the accelerated compared to contemporary groups, respectively, corresponding to 34 % advantage for accelerated over the contemporary group in the injured leg.

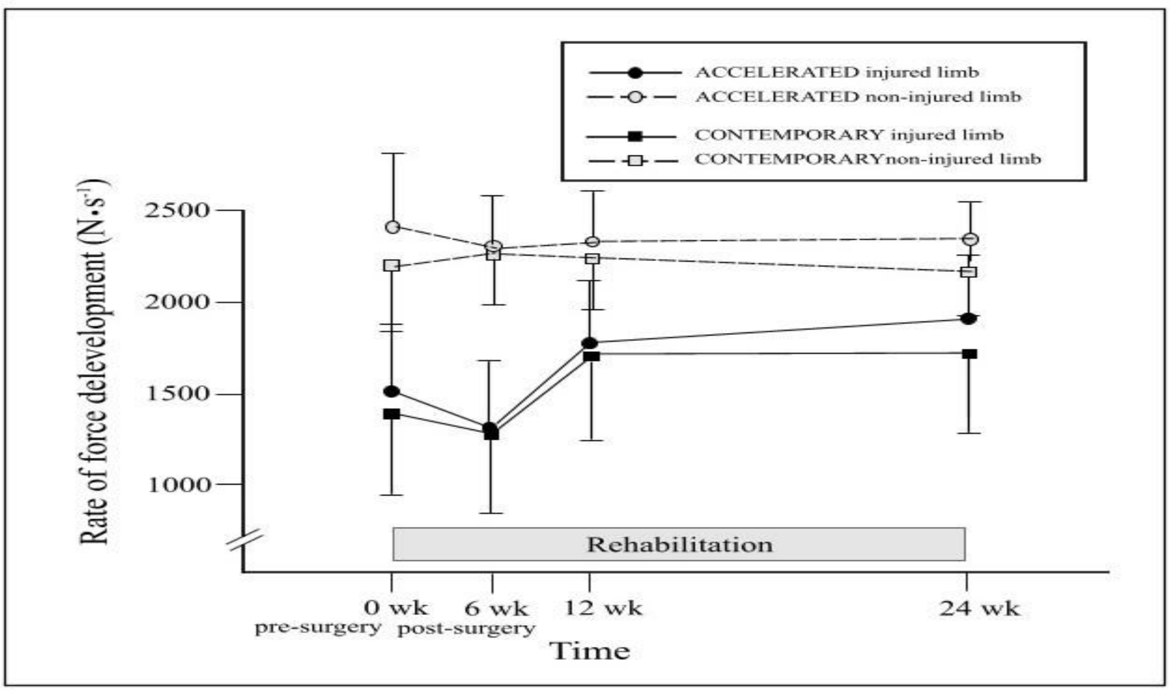


Figure 4.11: Rate of force development (RFD) of the knee quadriceps ($N{\cdot}s^{-1}$) of accelerated and contemporary groups for the injured and non-injured legs over time [from pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery].

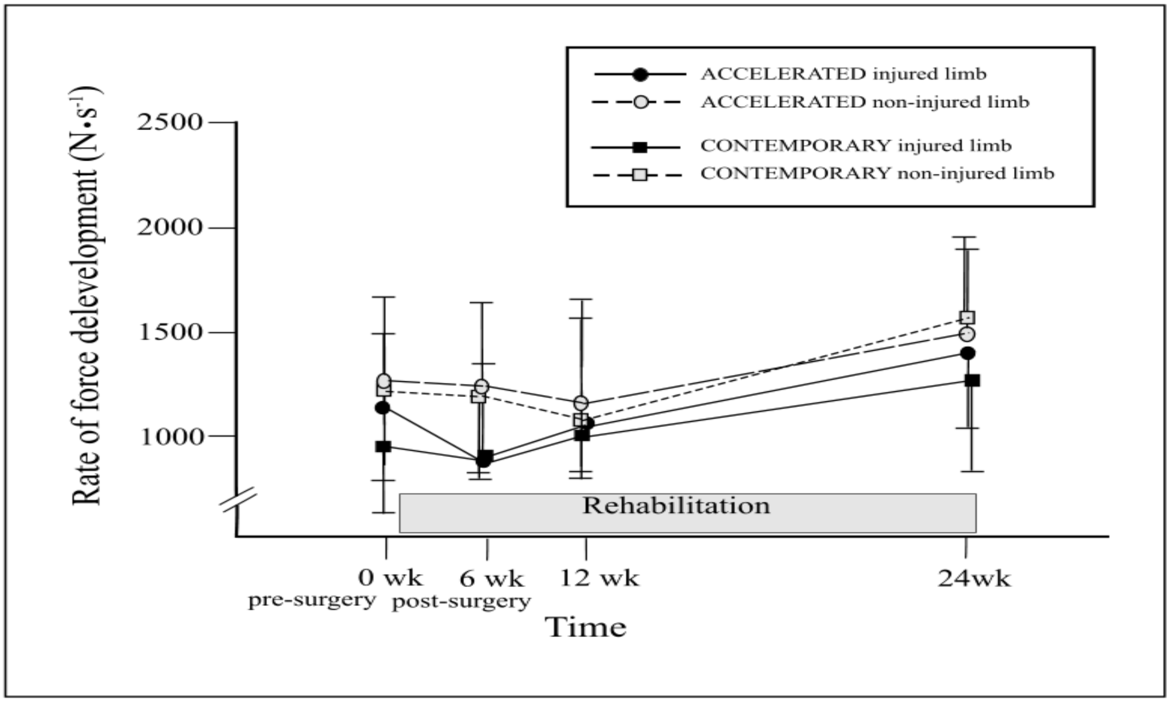


Figure 4.12: Rate of force development (RFD) of the knee hamstrings (N·s-[1]) of accelerated and contemporary groups for the injured and non-injured legs over time [from pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery].

Electromechanical delay (EMD) for quadriceps and hamstrings

Factorial ANOVA with repeated measures showed no significant group (accelerated; contemporary) by leg (injured; non-injured) by test occasion [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery] interaction elicited from the change scores for EMD of quadriceps musculature performance ($F_{(2.5,\ 96.2)\ GG}$=0.1; ns) and EMD of hamstrings ($F_{(2.4,\ 94.2)\ GG}$=0.2; ns). This pattern of non-significant interaction in change scores of EMD for quadriceps and hamstrings was also observed on two way factors (group by test occasion), indicating that the EMD of hamstrings and quadriceps of the injured and non-injured legs had not been differentially influenced over time. In addition, using ANCOVA (controlling for anthropometric and orthopaedic-related factors), no superiority in change scores of quadriceps and hamstrings EMD of accelerated group over contemporary group was suggested during any test occasion following ACLR surgery.

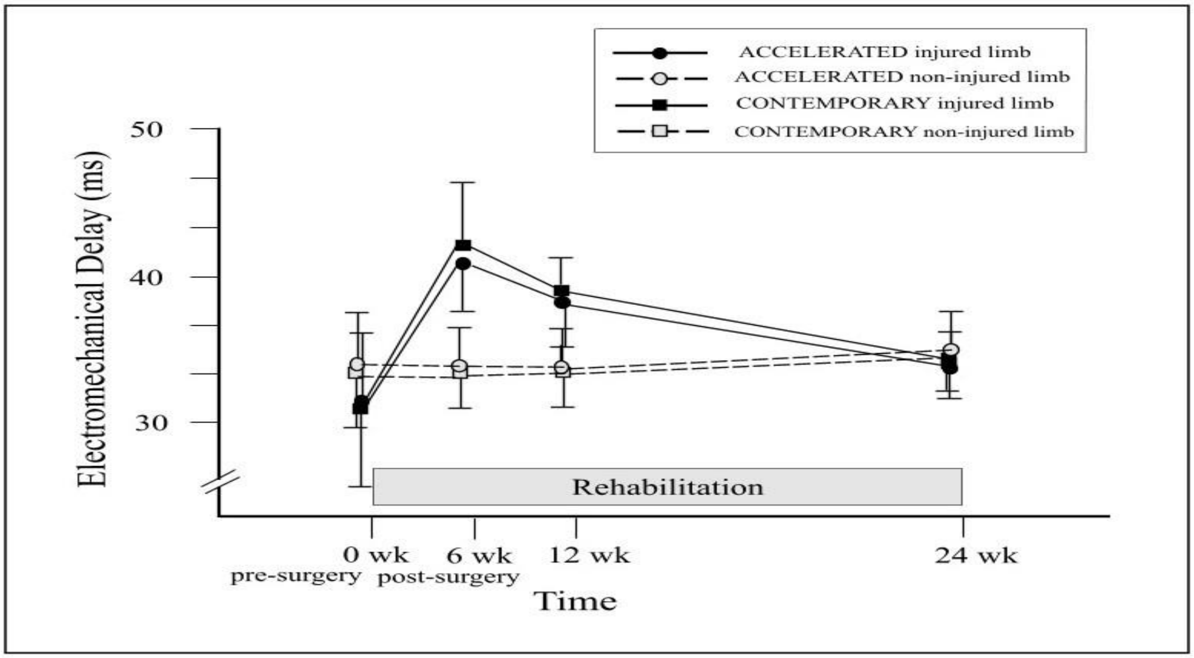


Figure 4.13: Electromechanical delay EMD (ms) of the knee quadriceps of accelerated and contemporary groups for the injured and non-injured legs from pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery.

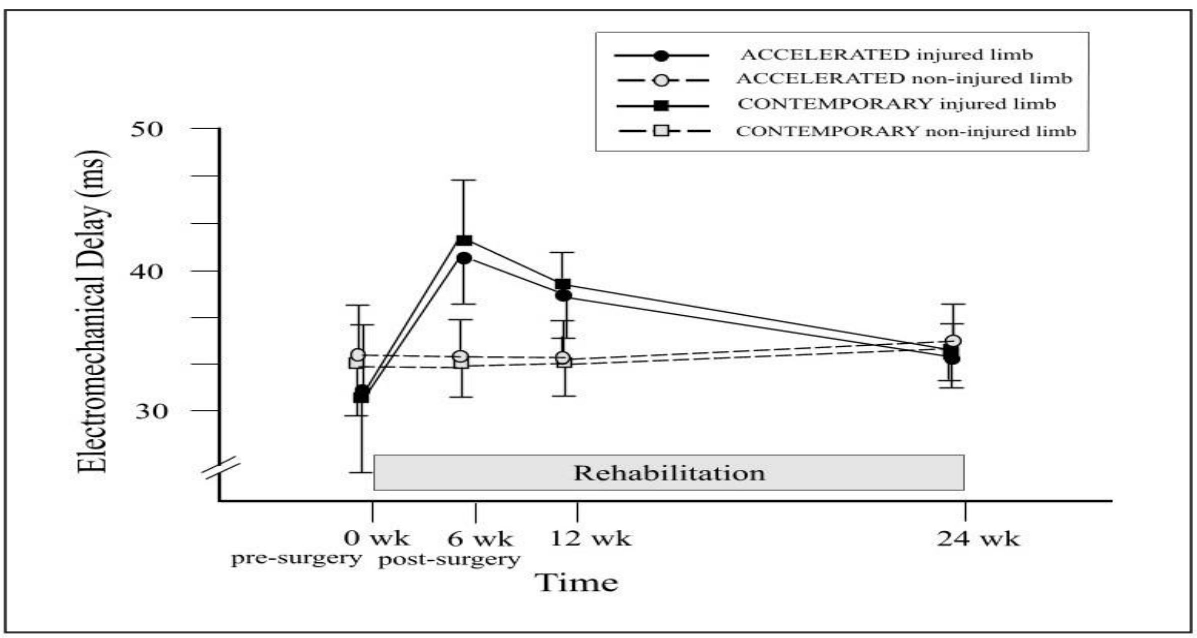


Figure 4.14: Electromechanical delay EMD (ms) of the knee hamstrings of accelerated and contemporary groups for the injured and non-injured legs from pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery.

Sensorimotor performance (SMP) for quadriceps and hamstrings

No significant group (accelerated; contemporary) by leg (injured/non-injured) by test occasion [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery] interaction using factorial ANOVA with repeated measures on the latter two factors was elicited from the change scores of objective SMP (force error) of quadriceps ($F_{(2.3,\ 89.5)\ GG}$=0.2; ns) and hamstrings musculature performance ($F_{(2.3,\ 89.1)\ GG}$=0.2; ns). This pattern of non-significant interaction in change scores of SMP for quadriceps and hamstrings was also observed on two way factors (group by test occasion), indicating that the SMP of hamstrings and quadriceps of the injured and non-injured legs had not been differentially influenced over time by accelerated conditioning. With the absence of observed interaction responses between the factors of group by leg by test occasions, the non-significant changes suggested that both groups rehabilitate to a level that's sufficient to avoid re-injury as demonstrated by the patterns of improvement in SMP performance over time following ACLR surgery. In addition, when controlling for the anthropometric and orthopaedic-related factors (body mass, unstructured physical activity and waiting time), no superiority in change scores of quadriceps and hamstrings SMP of accelerated group over contemporary group was found during any test occasion following ACLR.

Anterior tibio-femoral displacement (ATFD)

No significant group (accelerated; contemporary) by leg (injured/non-injured) by test occasion [pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery] interaction was observed using factorial ANOVA with repeated measures on leg by test occasion factors for change scores of ATFD ($F_{(1.5,\ 97.1)\ GG}$ = 0.6; ns). This pattern of non-significant interaction in change scores of ATFD was also observed on two way factors (group by test occasion), indicating that the ATFD of the injured and non-injured legs had not been differentially influenced over time by accelerated conditioning. Group mean change scores for ATFD suggested that while patients in both experimental and contemporary groups showed improved laxity at 12-24 weeks post-surgery, the accelerated rehabilitation conditioning provoked no significant improvement in knee laxity for both injured and non-injured limbs. Moreover, when controlling for the anthropometric and orthopaedic-related factors (body mass, unstructured physical activity and waiting time), no supriority in the decrease of ATFD in the accelerated group over contemporary group was suggested during any test occasion following ACLR surgery.

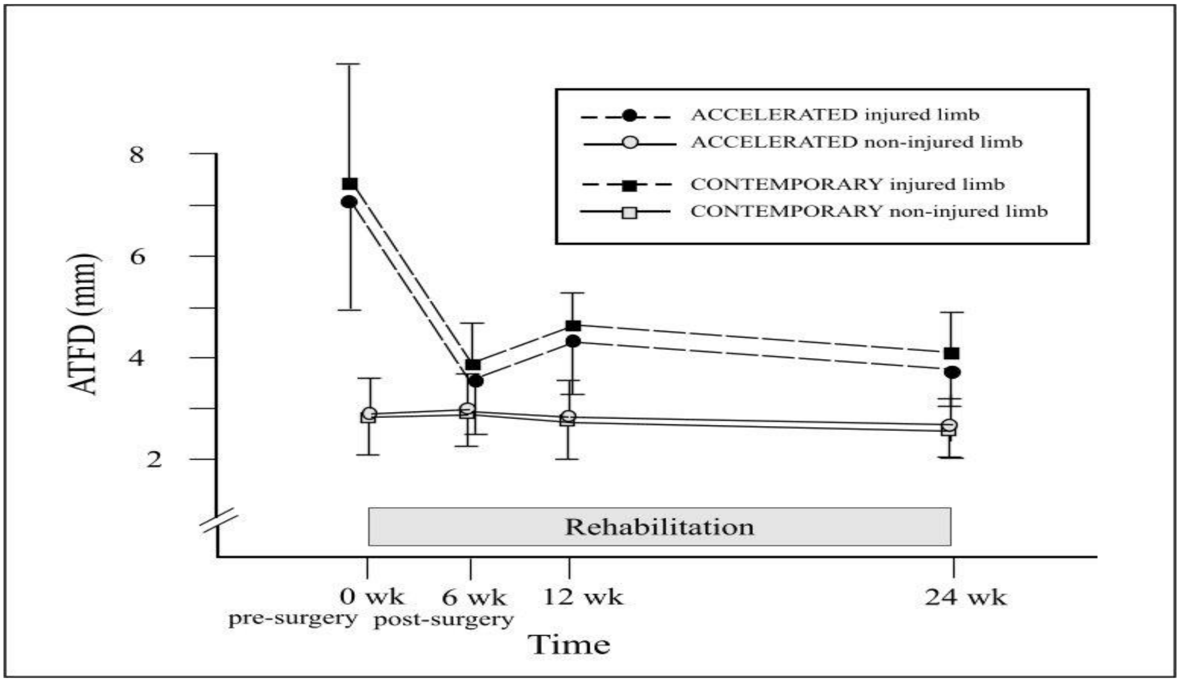


Figure 4.15: ATFD measurement (mm) scores of accelerated and contemporary groups for the injured and non-injured leg [from pre-surgery (0 weeks), 6, 12 and 24 weeks post-surgery].

Structured and unstructured physical activity

The means (mean±sd) for structured physical activity in accelerated and contemporary groups during the acute phase (pre-surgery-12 weeks post-surgery) of rehabilitation were 5.2±2.1 and 3.8±1.2 Kcalories.day^{-1}, respectively, while the means of the latter from week 12 to 24 was 3.8 3±2.1, 7±1.1 Kcalories.day^{-1}, respectively, for accelerated and contemporary rehabilitation groups, respectively. Using a one way ANOVA, there was a significant difference between the accelerated and contemporary group at pre-surgery-12 weeks post-surgery ($F_{(1,\ 38GG)}$ =167.3; p>0.01) and 12 to 24 weeks post-surgery ($F_{(1,\ 38GG)}$=213.7; p>0.01) in the structured physical activity, suggesting the loading exercises were superior in the accelerated group. This corresponded to 41 % and 30% advantage (higher increased frequency and intensity) at pre-surgery to 12 weeks and 12 to 24 weeks post-surgery, respectively, for the accelerated over the contemporary group.

	0 to 12 week post-surgery		12 to 24 week post-surgery	
	Mean (Kcalories.day^{-1})	SD	Mean (Kcalories.day^{-1})	SD
Accelerated	5.2	2.1	4.8	2.1
Contemporary	3.7	1.1	3.7	1.1

Table 4.7: Mean (± sd) of structured physical activity in the accelerated and contemporary rehabilitation groups (Kilocalories/day).

The mean scores of unstructured physical activity (home and leisure-based activity) were 226 versus 189 Kcal·day^{-1}at week 12, and 385 versus 335 Kcal·day^{-1}at week 24 post-surgery for accelerated and contemporary groups, respectively. There were no statistically significant difference between the two groups in terms of unstructured physical activity across all test occasions (one way NAOVA, $p<0.05$).

4.4 Discussion

The study of this chapter had introduced an accelerated conditioning programme in the acute phase (from week 1 to week 12) following ACLR surgery. The duration of the trial was 24 weeks in which the primary (single leg hop, IKDC, KOOS, K-SES and Lysholm) and secondary objective neuromuscular outcome measures (peak force, EMD, RFD, SMP and ATFD) of the study were recorded pre-surgery (0 weeks), iim6, 12 and 24 weeks post-surgery.

4.4.1 Principal findings of objective functional outcomes (single leg hop, IKDC, KOOS, K-SES, Lysholm)

The results of this study had shown no interaction responses (group by leg by test occasion) for the absolute scores of the single-leg hop test. There was also a lack of interaction using two way factors (group by test occasion), suggesting that the single leg hop performance of injured and non-injured legs had not been differentially influenced over time. However, the latter results indicated that accelerated conditioning had not adversely affected the objective functional outcome (single leg hop) of the accelerated group. The current study included patients who might be considered representative of the type of patients expected in the ACLR clinical population as they were randomly allocated into groups without the stratification of age, height, body mass and the level of structured and unstructured physical activities. Although the latter anthropometric and orthopaedic-related factors are known to have an influence on the outcomes of knee function following ACLR surgery (mentioned in the methods section), their features were not expected to directly influence the results of the current study. However, it was possible to statistically control for the latter factors for the purpose of investigating their influences on the outcomes of knee performance following ACLR rehabilitation. The justification for using the anthropometric and orthopaedic-related factors (age, height, body mass, waiting time to surgery and unstructured physical activity) has previously been mentioned in the introduction to this chapter. However, the specific aim of this trial was to investigate the clinical efficacy of accelerated conditioning (i.e change scores from pre-surgery to 12 weeks and 12 to 24 weeks post-surgery) and the rate of responsiveness in the performance indices of knee quadriceps and hamstrings of the non-injured and injured limbs following ACLR surgery.

When adjusting for orthopaedic-related factors (waiting time, body mass and unstructured physical activity), significant interaction responses had been observed for the change scores of single leg hop performance with superior scores in the accelerated over the contemporary group at pre-surgery to 12 weeks post-surgery. The percentage change scores for the accelerated and contemporary groups were 12% and 10%, respectively in the injured legs. This same finding could have possibly been observed at week 6 post-surgery had the testing for single leg hop been assessed. Although moderate improvement in single leg hop performance was observed in the latter period, the extent of percentage change for the accelerated (advantage gain of 2% in injured leg) over the contemporary group might be considered insufficient to justify the changing of care delivery for patients with ACLR surgery. However, this study had reported LSI mean scores of 110.8%, 113.5 %, and 112.7 %, 113.8 % for the accelerated and contemporary groups at 12 and 24 weeks post-surgery, respectively. These percentage changes are higher than those recommended by Reid et al. (2007) as criteria for full return to physical activity [equal or more than 85% of LSI represents normal knee function). Although the percentage change scores between the accelerated and contemporary group were small at pre-surgery to 12 weeks post-surgery (2%), the individual differences within the accelerated and contemporary groups in the latter period had not exceeded the MCID that had been suggested in the literature (5% as the cut-off point for minimal clinically important difference in LSI single leg hop, Reid et al. (2007)]. This indicates that it was not possible in both groups to separate the participants who had shown improvement from those who had not in the objective functional outcome of the single leg hop test. In general, the implication of the current finding indicates that the accelerated conditioning had not adversely affected the objective functional outcome (single leg hop) of the accelerated group during the acute phase of rehabilitation. It is plausible that improved outcomes of the single hop performance could have been observed if the accelerated conditioning continued beyond 12 weeks post-surgery. However the latter conditioning was withdrawn by week 12 post-surgery in order to minimise the unequal iso-volumetric exercise dose between the accelerated and contemporary group.

With respect to the IKDC (subjective functional outcome measure), there was no significant difference between the two groups in the change scores (pre-surgery to 12 and 12 to 24 weeks post-surgery) for IKDC inventories. Although the latter questionnaire had shown to be reliable and reproducible in this study (Appendix VI), the IKDC scores might be interpreted as lacking sensitivity (i.e. the ability to detect a clinically relevant difference in patient's outcome measure) in the acute phase of rehabilitation in the current study. This view is shared by Risberg et al. (2009) who had shown that IKDC was not responsive in the acute phase of rehabilitation following ACLR surgery. With regards to MCID, Collins et al. (2011) and Greco et al. (2010) reported the MCID for IKDC to be 6.3 at 6 month follow up, and 16.7 points (95% confidence interval) at 12 month follow up in patients with knee surgical procedures. The current study had exceeded the values of MCID suggested in the literature as the values of 11.4 and 13.2 points were reported at 12 weeks, and 24.4 and 22.2 points at 24 weeks post-surgery in the accelerated and contemporary groups, respectively (i.e. between group differences). This indicates that it was possible to differentiate between participants who perceived themselves as "improved" from those who did not in both groups at 12 weeks post-surgery.

Although Lysholm and K-SES questionnaires had shown to be reliable and reproducible in the literature, there was no significant difference between the two groups in the change scores of Lysholm and K-SES inventories of this study. While Beynnon et al. (2005, 2011) had shown no significant difference in KOOS scores between the accelerated and non-accelerated groups in all test occasions following ACLR surgery, the results of this study were consistent with the findings of Roos and Lohmander (2003) who reported significant improvement in the sub-section of KOOS (QOL; Quality Of Life) at 6 and 12 weeks post-surgery. In addition to the significant interaction observed in the current study at pre-surgery to 12 weeks post-surgery in KOOS (sub-section of quality of life), the sub-section of pain had shown significant improvement in the latter test occasions. With regards to MCID of KOOS, the review of Collins et al. (2011) and the study of Roos and Lohmander (2003) reported 6-12 and 10 unit points, respectively, of improvement across all five sub-sections to represent the cut-off points for KOOS sub-sections at 6 months following ACLR surgery. However, the results of this current study were consistent with those reported in the latter two studies as scores of 3.4 and 6.4 points at 12 weeks, and 5.8 and 7.5 points at 24 weeks post-surgery were observed for KOOS (P) in the accelerated and contemporary groups, respectively. Similarly, KOOS (QOL) had shown the values of 3.5 and 3 points at 12 weeks, and 6.5 and 5.8 points at 24 weeks post-surgery in the accelerated and contemporary groups, respectively. This implies that it was possible to differentiate between participants who perceived themselves as “improved” from those who did not in both groups at 24 weeks post-surgery.

Even though all the patient-reported outcome measures used in this study (i.e. K-SES, Lyhsolm, KOOS and IKDC) were reported to be reliable, sensitive and valid, based on the results of the current study, it seems that KOOS have better sensitivity than the latter questionnaires in the assessment of patients with ACLR surgery and their subsequent rehabilitation. This was evident in the study of Nau et al. (2002) who used both IKDC and KOOS instruments to assess patients’ perceptions following ACLR surgery and found that while IKDC scores did not show any difference between a group who had a BPTB graft and a group who had Ligament Advancement Reinforcement System (LARS) artificial ligament, the LARS group had showed better results in all the subscales of KOOS at one year follow up. It is likely that while the other questionnaires used in this trial aggregate the scores of all the domains into one score, KOOS separates them in order to gain a better understanding of the true contribution of each domain (i.e. physical activity) in the assessment of knee function.

4.4.2 Principal findings of objective neuromuscular measures

Quadriceps and hamstrings

As part of accelerated rehabilitation, this current study emphasised increased dosage (frequency and intensity) for the leg curl, isometric quadriceps, OKC leg extension, seated leg press and mini squatting exercises in the period between week 1 and week 12 post -surgery in the accelerated conditioning group (Table 4.2). Quadriceps weakness following ACLR surgery might have serious adverse effects and can play an important role in determining the physical knee disability following the latter surgery (Heijne and Werner 2007).

Even though previous studies had demonstrated that the accelerated group had significant improvement in thigh muscle strength (knee flexors and extensors) at 3 month follow-up (Beynnon et al. 2011) and significantly greater isokinetic strength in the quadriceps at 4 month follow-up (Tagesson et al. 2008, Shelbourne and Nitz 1990), the results of this study revealed that quadriceps muscle strength, in particular, did not show any interaction responses (group by leg by test occasion). Instead, in the context of ACLR rehabilitation, the results inevitably put the importance of quadriceps strength under scrutiny. In addition, because this trial combined OKC and CKC quads exercise, the results however were incongruent with those of Mikkelsen et al. (2000) who found that combined the CKC and OKC group had a significantly better improvement in quadriceps strength with no increased in laxity measurements than the CKC exercise group alone at 6 month period following ACLR surgery. In fact, a better improvement would have been expected in this trial as it introduced a longer accelerated intervention period (12 weeks) compared to that of Mikkelsen et al. (2000) [6 weeks intervention].

On the other hand, although 92% of patients in this study had a hamstrings graft, interestingly there were consistently significant improvement in hamstrings muscle strength for the accelerated group when adjusting for body mass, unstructured physical activities and waiting time between pre-surgery to 12 weeks post-surgery. Given that the majority of participants had a hamstring graft, it is plausible that hamstring musculature had experienced more deconditioning than quadriceps following the surgery, and that the superior gains of hamstring peak force at 12 weeks post-surgery might be due to the quicker recovery demonstrated in the hamstrings compared to quadriceps following the effects of accelerated conditioning in the acute phase of ACLR rehabilitation.

RFD and EMD for quadriceps and hamstrings

The most notable result in the RFD performance change scores was that while quadriceps had shown no interaction responses when adjusting for orthopaedic-related factors (body mass, unstructured physical activity and waiting time), hamstrings continued to show significant improvement in RFD with a 34 % advantage over the contemporary group between pre-surgery to 12 weeks post-surgery in the injured leg when controlling for the latter factors. RFD has been used extensively to evaluate the capacity of generating muscular force at a rapid rate and the evaluation of RFD is considered an essential component of functional tasks including postural balance as well as sports performance (Aagaard et al. 2002). The possible explanation for the observed significant interaction response (group by leg by test occasions) in the hamstrings and not in the quadriceps might be similar to the explanation given regarding the observed improvement in the peak force of hamstrings (quick recovery following the deconditioning that was influenced by the harvesting of hamstring graft).

On the other hand, when adjusting for body mass, waiting time and unstructured physical activity, this pattern of change scores in the latter period however had not been observed in the EMD performance change scores in both the quadriceps and hamstrings musculatures of the injured and non-injured legs. The lack of EMD interaction in the study is incongruent with the results of Gleeson et al. (2008) who reported a significant increased performance of EMD at week 6 post-surgery in the knee hamstrings of the injured leg, with an impressive relative effect size of 1.8 compared to pre-surgery scores. As mentioned earlier in the methods section, EMD regulates neuromuscular reaction time which is required during forces of unrestricted development and sufficient magnitude that are capable of damaging ligamentous tissue in synovial joints (Gleeson et al. 2005). The lack of signification interaction responses (both using three and two way factors) of EMD in the current study might be due to the fact that accelerated as well as contemporary conditioning was not designed to influence reaction time to stimulus that had been adversely effected by ACLR surgery (impaired proprioception and greater elasticity in the series elastic component of the harvested area.) However it is worth investing whether disassociation between the RFD, EMD and SMP and peak forces over time of rehabilitation period might have any adverse effects on the outcomes of knee.

SMP (force error) for quadriceps and hamstrings

There was an absence of observed interaction responses (both on three and two way factors) in the change scores (pre-surgery to 12 and 12 to 24 weeks post-surgery) of objective SMP (force error) for both quadriceps and hamstrings. Given the importance of SMP in mimicking the process of muscle re-education following the disruption to the neuromuscular system as a result of surgical intervention (e.g. ACL rupture), the non-significant interactions might be explained by that ‘accelerated’ conditioning was not ‘specific’ enough to improve the SMP performance that is positively influenced by proprioceptive training (Cooper et al. 2005). On the other hand, it is plausible that both programmes are similarly responsive (with and without specificity) in respect of SMP and that both groups rehabilitate to a level that is sufficient to avoid re-injury given the long-standing success rate of the physiotherapy programme associated with RJAH hospital in Oswestry.

ATFD (knee joint laxity)

This study found no superiority of accelerated group over the contemporary group in the decrease of ATFD between pre-surgery to 12 and 12 to 24 weeks post-surgery using three (group by leg by test occasions) and two way factors. However the extent of the change scores in knee ATFD in this study matched those patterns reported in the literature particularly in the acute phase (12 weeks post-surgery) of ACLR rehabilitation (Gleeson et al. 2008, Kvist 2004). Given that the acceleration of full weight bearing, full ROM and OKC quadriceps were prescribed for the accelerated group in this study, the reason the latter group had not shown statistically significant better knee stability (i.e. a decrease in ATFD) over the contemporary group is not fully understood. This was consistent with the finding of Wojtys and Huston (2000) who thought that the knee laxity assessment at 6 month follow up did not inform about the knee functional status as it demonstrated a similar level of tightness to the contralateral side 6 months following ACLR surgery. This view is supported by previous long-term follow-up studies of ACLR that demonstrated achieving normal or near normal knee joint laxity scores takes longer than 24 weeks post-surgery (Øiestad et al. 2010). Wojtys and Huston (2000) also observed no correlation between ATFD and any other objective or subjective measures of knee function following ACLR surgery. However, the current study had not expected a significant difference between the two groups in terms of decreased knee laxity as the accelerated conditioning was not been designed to mechanically load the ACL bur rather to increase the responsiveness in functional and physical performances through the ‘acceleration’ of rehabilitation. Indeed the current finding had confirmed that no adverse effect had been associated with the accelerated group in terms of the integrity and stability of ACL.

In summary, it might be plausible that the trend of relative effect sizes for the changes in the performances of the functional (single leg hop and patient-reported outcome measures) and objective neuromuscular outcomes over the period of 24 weeks follow-up was influenced by two main factors; the heterogeneity of dose-response conditioning prescribed for each study group in the early phase of rehabilitation and the absolute change of scores over time in the latter outcomes. For instance, as reported in the results section, there was a significant difference in the loading (increased frequency and intensity of exercise stress) between the two groups in the change scores of 0-12 versus 12-24 for structured patients’ endeavours, corresponding to a 41 % and 30% advantage (higher increased dosage) at pre-surgery to 12 weeks and 12 to 24 weeks post-surgery, respectively, for the accelerated over the contemporary group. This suggests that the extent of improvement in the acute phase due to increased dosage was accompanied by less gain at the 24 weeks post ACLR surgery in both groups. In summary, the statistically significant interaction observed when controlling for waiting time, body mass and unstructured physical activity, the latter interaction might also be clinically meaningful for patients as demonstrated in the MCID scores of KOOS and IKDC.

4.4.3 Strengths of the study

Quantifying structured physical activity

While previous studies assessed compliance based on the number of sessions attended and not the dosage of exercise, the current study had quantified the sessions attended from a dose-response perspective. To the knowledge of the author of this thesis, to date no study has quantified the dosage of exercises endorsed in ACLR rehabilitation. In addition, the trial had also verified the successful experimental manipulation of treatment which included early ROM, weight bearing and isometric and OKC quadriceps within the accelerated rehabilitation programme. The quantification of structured physical activity had offered the current study an advantage in investigating whether or not there were significant gains in the functional and physical performance outcomes during the presence of stimulus (increased dosage of exercise stress at the acute phase) and after the ‘withdrawal’ of the stimulus or dosage. As a result, the latter investigation had allowed the current study to consider whether or not the dosage introduced in the accelerated conditioning group can be considered clinically substantive.

The mean scores for unstructured physical activity in the accelerated and contemporary groups were 226 versus 189 Kcal·day^{-1} at 12 weeks, and 385 versus 335 Kcal·day^{-1} at week 24 post-surgery, respectively. Although no significant difference was observed between the two groups (one way ANOVA) across all test occasions, nevertheless, an investigation on the relationship between the change scores of the unstructured physical activity and the structured physical activity was deemed important in order to understand the contribution of both physical activities on the outcomes of knee performance (chapter five). In addition, the relationship between the change scores of the unstructured physical activity and the objective measures of knee had been explained in the next chapter (chapter five) in order to investigate the influence of the latter anthropometric factor on the objective outcomes of knee function.

The use of isometric and not isokinetic dynamometry

Although the majority of studies (Liu-Ambrose et al. 2003, Tagesson et al. 2008, Shaw et al. 2005, Beynnon et al. 2011) investigating knee outcomes following ACLR surgery used isokinetic dynamometry for assessment, its validity is only justified during sport-specific activity where muscles are in a state of isotonic action. However during muscle function, the force produced is a result of combined isometric and isotonic actions. Even though the isotonic dynamometry showed content, face and construct validity (Clark 2001), it can be argued that isokinetic dynamometry results lack the validity to measure `functional' muscle strength (physiologically based criteria-related validity). Evidence in support of this suggestion has been presented in the literature that demonstrated the relatively weak to moderate relationship existing between the functional performance test and isokinetic strength of thigh muscles (Clark 2001). It was therefore due to the latter factors which led the author of the current study to choose isometric testing over isokinetic to test muscle strength. Isometric testing has an advantage in that it mimics the pattern of ACL injury that involves slight knee flexion in a static position (Silva et al. 2012, Silvers and Mandelbaum 2007).

4.4.4 Study limitations

Definition of "accelerated rehabilitation"

It was difficult to determine the definition of "accelerated rehabilitation" and its components as discussed in detail in the systematic review of chapter two. Therefore due to lack of consensus within the literature, the investigator of this trial was not able to include all the accelerated exercises prescribed in previous robust studies (i.e. RCT with high Pedro scores, chapter two). Over the last decade, there has been a shift in the literature from studies drawing a comparison between two rehabilitation programmes (6-9 months versus 4-6 months) to a comparison between different rehabilitation programmes (e.g. proprioception versus strength) of the same length (4-6 months). The latter comparison is based on accelerated rehabilitation which principally includes early full weight bearing, ROM and isometric OKC quadriceps (Shelbourne and Klotz 2006, De Carlo and McDivitt 2006). However, De Carlo and McDivitt (2006) argued that the term accelerated rehabilitation" is no longer appropriate and can be misleading given that all ACLR rehabilitation programmes are currently based on a 4-6 month period. According to the latter authors, the time frame of each phase of ACLR rehabilitation should be determined by both clinical experience and individual response to the programme. From the clinical perspective, accelerated rehabilitation should be also be based on the dose-response of the accelerated conditioning prescribed in each phase of ACLR rehabilitation, and that progression should be based on achieving the goals of each phase. However this trial had made a novel attempt to replicate previous studies (Beynnon et al. 2005, 2011) and thus had introduced increased frequency and intensity of exercise stress in the early phase of the accelerated rehabilitation group.

Minimal clinical important difference (MCID) for knee outcome measures

Although MCID for the primary functional measures (KOOS, IKDC, single leg hop) and the secondary outcome measure ATFD in this study could be compared with those reported in the literature, the current study had not been able to assess the MCID for PF, RFD, EMD and SMP as the MCID of the latter measures have not been reported the literature presumably because of the ‘correlational’ rather than ‘causal’ nature of the evidence relating each measure of physical performance to functional capability. This makes it difficult to confirm the values that might be deemed clinically relevant to both patients as well as physicians and therapists.

Single leg hop as a primary outcome for knee functional performance

Along with IKDC, the current study had chosen the functional single leg hop test as a primary outcome. This was based on previous studies (Perry et al. 2005, Reid et al. 2007, Clark 2001) which showed that the latter test was reliable, valid and used as a primary outcome in the assessment of knee function following ACLR surgery. However, based on previous laboratory kinematic and kinetic works of Blackburn and Morrissey (1998), the contribution of horizontal performance in determining knee function was 3.9% compared to 49 ± 56% of vertical performance. Given these biomechanical data, the authors concluded that the single leg hop test might not be the best test in terms of criteria-based validity in the assessment of knee function. However it can be argued that the selection of validity test could be either based on the contribution of the knee joint to specific tests such as the single leg hop, or that validity could be based on the ability of the functional test to determine between limb differences (i.e. LSI). Because the current study had assessed both factors, it is plausible to say that the functional single leg hop test might have been an appropriate choice for assessing the outcomes of knee function in this trial. To enhance the justification for using the single leg hop test, chapter five will assess whether the latter test had the most influence amongst other tests (neuromuscular and patient-reported outcome measures) or if indeed it had the strongest relationship (i.e correlation) to the successful outcome of ACLR rehabilitation. Additionally, this current study had not observed significant interaction in the accelerated and contemporary group in LSI single leg hop, suggesting that contralateral limb (non-operated knee) might have experienced deconditioning due to the waiting time for surgery.

4.4.5 Clinical implications

It might be perfectly justifiable to investigate accelerated rehabilitation in the current study as previous studies had shown that early weight bearing was effective in lowering the incidence of anterior knee pain (Kvist 2004), and the isometric quadriceps exercises in the first 2 weeks post ACL surgery improved knee ROM (Shaw et al. 2005) while regaining full knee extension reduced the chances of developing flexion deformity (De Carlo and McDivitt 2006).

Even within a well-established, successful, and some would say ‘already accelerated’ programme of ACLR rehabilitation, it is still possible to significantly enhance functional and physical performance-related outcomes. Improvements occur concomitantly with the period of earlier weight-bearing, full weight bearing and increased dosage of exercise stress (0-12 weeks) but the responses of patients do not carry-over beyond the cessation of loading and cannot be seen by the end of formal and structured rehabilitation (24 weeks). Thus, at the very least, this type of ‘accelerated’ intervention has been successful with no adverse patient’ episodes during treatment and outcomes that at least match those of the current contemporary practice. One of the advantages of the current study was the verification of the increased frequency and intensity of exercise stress (dosage) associated with ‘structured’ rehabilitation and thus greater precision had been obtained with response to the latter dosage. In addition, the unstructured’ physical activity (home and leisure-based activity) of exercise stress had also been quantified in an attempt to quantify the overall dosage of exercise-related stress during ACLR rehabilitation. The significant gains in functional and physical performance outcomes of 12% before the ‘withdrawal’ of the experimental stimulus, would be considered clinically substantive (Bailey et al. 2003). If these levels of improvement and enhanced clinical efficacy could be maintained or enhanced further with continued ‘accelerating’ rehabilitation strategies during weeks 12 to 24 of the programme of care, it would be expected for such practices to be incorporated into contemporary clinical care pathways.

Moreover, when controlling for the factors of body mass, waiting time and unstructured physical activity, the presence of significant interaction in the accelerated group at the acute phase and the lack of such interaction at the late stage of rehabilitation suggests two main things; 1) that the accelerated rehabilitation had a superior advantage over the contemporary programme of ACLR at the time of intervention (weeks 1-12 post-operatively), and 2) orthopaedic-related factors were influential in determining the outcomes of ACLR rehabilitation. Given that there was heterogeneity in the patterns of response (up to 12 weeks) amongst the outcome measures that were supposed to be measuring the functional responses (i.e. objective single leg hop and subjective patient-reported outcome measures), it was imperative that the aim of the subsequent phase of this trial was to illustrate the important the relationship amongst them as well as their clinimetric qualities of the outcome measures. Appendix VI gives full details of the clinimetric qualities of the knee outcome measures.

Unanswered questions and future directions

The "accelerated rehabilitation" endorsed in the current study did not consider the pre-operative rehabilitation phase as part of the ACLR rehabilitation programme. According to De Carlo and McDivitt (2006), there is a trend of introducing pre-operative rehabilitation for the purpose of better management of knee swelling as well as maintaining good ROM before surgery. To the knowledge of the author, no published studies have assessed the outcome measures associated with pre-operative rehabilitation of the accelerated programme. Therefore future studies could enhance the understanding and contribution of such rehabilitation in the successful outcomes of ACLR rehabilitation.

In addition, although this trial examined patients' progression from one phase of ACLR rehabilitation to another in terms of the achievement of neuromuscular performances, future studies should focus on the evaluation of patient's psychobiological status using patient-reported outcomes. It is plausible that greater delays to the progress of the subsequent and advanced phases of rehabilitation could be due to the psycho-physiological status of the patients. Patient with ACLR might experience negative psychological factors reflected in their self- perceived performance capability which in turn could lead to physical and psychological detrimental responses to both rehabilitation and return to full function of the knee joint. The capability of self-perception is becoming increasingly important in tailoring the progress of rehabilitation and the return to pre-injury levels (Beynnon et al. (2005, 2011). Therefore evaluation of the latter factors (self-perception) will help therapists to design treatment plans better and according to patients' need during ACLR rehabilitation especially in the case of discrepancy (disassociation) between the objective outcomes and the subjective measures (patient-reported- outcomes) during routine tests occasions.

4.5 Conclusion

In conclusion, good clinical results had been demonstrated in the current study with improved PF and RFD of hamstrings and KOOS (quality of life and pain) in the acute phase of rehabilitation (12 weeks post-surgery). Although accelerated rehabilitation had not appeared to have any adverse effects on achieving successful outcomes following ACLR surgery, the changing of care delivery on the basis of a 2% advantage gain in the single leg hop performance of the injured leg (primary outcome) for the accelerated conditioning group is not justifiable. However, the patterns of improvements in the functional, neuromuscular and patient-reported outcomes during the acute phase (1-12 weeks) appear to show positive clinical effectiveness of accelerated rehabilitation which in turn might help to improve the standard practice of physiotherapy in ACLR patients.

5 Chapter Five (Study Two)

Correlates of Knee Functional Outcomes of Patients Following Anterior Cruciate Ligament Surgery and Rehabilitation

5.1 Introduction

In order to effectively assess clinical intervention, it is important to employ standardised outcome measures that can offer evidence-based practice and knowledgeable resolution regarding therapy (Reid et al. 2007). In addition to objective neuromuscular measures, subjective patient-reported measures of knee function are often employed within a clinical setting to assist in observing the development of rehabilitation following ACRL surgery (Adams et al. 2012). A significant basic idea would be that patient's perception of functional capability is similar to that of objective assessment. Disassociation among objective and subjective measures of capability related to functional performance could be hypothesised to incite sub-optimal conditioning within rehabilitation therapy with the mismatching of perception and objectivity resulting in the underestimation or overestimation by patients of sense of endeavour and the amount of exercise with compromised results. Comprehending the sequences of association in neuromuscular performance (objective) and individual's own perception (subjective) and the association of every one with knee functional capability could provide vital understanding of the relationship between perceptual measures of patients and the physical capability obtained from objective assessment (Hewett et al. 2005). Moreover, any association found between functional performance and objective/ subjective measures could correctly inform the hierarchy of significance amongst neuromuscular and perceptual aspects of a patient that have to be observed during rehabilitation programme to ascertain improved functional results. As yet it is not known which assessment measure (whether subjective and objective) is most pertinent. For instance, which measurement offers the most suitable association to the functional capability of the knee joint, or which measurement may be employed to predict the functional capability of the patient to go back to physical or sporting activity (Mikkelsen et al. 200, Beynnon et al. 2011) ? Moreover there is very little evidence from the literature on whether a relationship (correlation) exists between the objective and subjective measures of knee capability following ACLR surgery. Finally, the question of whether early change of scores of measures (be it objective or subjective) can actually predict the late change of scores has not been addressed in the literature (Liu-Ambrose et al. 2003).

The Knee Injury and Osteoarthritis Outcome Score [KOOS], the Lysholm Knee Rating System, the Knee Self Efficacy Scale (K-SES), and the International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC) comprise a range of questionnaires designed to quantify patient-reported outcomes of knee function, and which necessitate the patient to declare their symptoms and physical capability. Objective measures of functional capability, like muscle power, EMD, RFD, knee laxity and sensorimotor performances are regarded as the main indicators of optimal treatment and of suitable timing for the patient to determine the readiness to go back to full physical and sporting activities (Fitzgerald 2000).

The studies of Borsa et al. (1998) and Ardern et al. (2011) had shown that patients displaying less variation in objective functional performance among injured and uninjured contra-lateral limbs (>85% of uninjured limb operation) were observed to be more likely to return to sports compared to those displaying greater variations (<85% of uninjured limb). In contrast the latter author had shown that patients self-reporting regular or almost regular knee function using IKDC inventory (93% of test population) were not very likely to go back to competitive sport compared to patients declaring poor operation [7% of test population]. The utilization of the contra-lateral asymptomatic leg as a reference and control is common, and is employed in this manner for the intervention research of this current study. However, cautions exist for the unlimited employment of the contra-lateral limb as a basis for the injured limb due to the possibility for deconditioning related to injury-associated changes that resulted from reduced physiological loading, bi-lateral neurophysiological deconditioning as well as limb dominance differences (Gleeson 2008). However, the idea of functional symmetry amongst injured and uninjured limbs has been preferred within the literature (Borsa et al. 1998, Ardern et al. 2011, Thomee et al. 2011) with patients who display an acceptable extent of symmetry (85-100%) are regarded as more likely to return to both demanding physical activities and competitive sports (Lentz et al. 2012, Ageberg et al. 2008).

5.1.1 Correlation between objective and subjective measures in ACLR rehabilitative setting

The researcher of this thesis had reviewed some of the evidence from the literature that investigated the relationship between objective neuromuscular and subjective patient-reported outcome measures in order to identify the hierarchal order of determinants of knee functional performance following ACLR surgery and rehabilitation. Associations connecting hop test marks and patient-reported measures of knee function, offered by KOOS, Tegner activity scale, Lysholm and IKDC measures, were declared in several studies. However, the only two studies to link between patient-reported measures and objective measure of knee function was amid IKDC with single leg hop within the research of Sernert et al. (1999) [r=0.28, n=527] and Logerstedt et al. (2012) [Odd ratio 1.05 (95% confidence interval), p<0.02, n=120]. In the former study, there was a disparity separating the physical rehabilitation results (e.g. knee ROM, steadiness, hop tests) and the rate of return to sport. Over 85% of contributors had regular or almost regular knees at follow-up, as quantified by the IKDC form, even though there was no association linking IKDC and the rate of return to sport. Nonetheless, patients having a hop-test limb symmetry index (LSI) comprising below 85% were considerably less likely to have tried sports when contrasted to patients having an LSI comprising 85% or above. Therefore, the association linking knee function and successful rehabilitation outcome is still not clear, as with IKDC no association was established, although with the hop test there was a link to return-to-sport results. Consequently, the association linking functional knee capability and return to sport necessitates supplementary exploration (Ardern et al. 2011).

On the other hand, while the study of Logerstedt et al. (2012) reported that hop tests were not predictors of postoperative outcomes, conducting hop tests six months after ACLR surgery was predictive of subjective knee function (IKDC) after one year. However, the number of patients who completed the 6 months to one year hop tests was reported to be small. In addition, since the study had included actively young population, it is not possible to generalise the results to other age group population.

The study of Sernert et al. (1999) had recognised associations linking single hop test scores and sagittal knee joint laxity quantified by KT-1000 (a knee arthrometer) [r= -0.08, n=527]. In contrast, the results of Kocher et al. (2004) proposed weak or negative association linking the instrumented knee laxity and patient satisfaction (r= 0.05), work level (r= 0.01), sports level (r= -0.05), functions of daily living (r = -0.02) and Lysholm score (r= -0.04)]. In addition, the study of Snyder-Mackler et al. (1997) and Kocher et al. (2004) were not able to find a correlation between knee laxity and subjective measures of the knee. Interestingly, Lavoie et al. (2000) established that despite clinical results showing that 85% of patients had Lachman > 3 mm as well as 44% had positive pivot shift, none of their patients (59 patients) necessitated a second knee surgery. This implies that what was regarded as a poor or fair outcome (objective) by the surgeon could be satisfactory for the patient (subjective patient satisfaction). Figure 5.2 shows the correlation between objective and subjective measures of the knee.

Hurd et al. (2008) explored the hop test as a physical performance measure of knee function and as a forecaster of dynamic knee stability. The study declared poor numerical associations linking single hop test results and knee laxity. However, moderate association linking quadriceps strength and knee function was reported on the latter study [coefficient of determination; r^2 = 0.04-0.08]. An alternative research sustaining the latter association was done by Liu-Ambrose et al. 2003, who displayed that quadriceps strength was a determining factor of knee functional capability with a remarkable association of r= 0.85. On the other hand, Wojtys and Huston (2000) had shown that hamstring strength came second after quadriceps strengths with regards to best predictors of knee functional performance, although r^2 value of this relationship was not offered in the latter study. With regards to proprioception, significant association connecting hop test scores and knee joint position sense (i.e. proprioception) was determined in one of the researches by Borsa et al. (1997) [r=-0.56, n=29]. No evidence was found from the literature between knee functional performance and EMD or RFD or sensorimotor performance.

On the other hand, Sernert et al. (1999) and Kocher et al. (2004) had investigated more on the relationship between various patient-reported outcome measures (subjective) in clinical population of ACLR surgery. Based on the latter two studies, significant correlation was found between IKDC and Lysholm (r = 0.66), and between subjective patient satisfaction and IKDC and Lysholm. No evidence from the literature on the correlation between KOOS or K-SES with other patient-reported outcomes.

In summary, Table 5.1 and Figure 5.1 and 5.2 illustrates a summary of all studies reviewed from literature on relationship between the knee measures (both objective and subjective) and knee functional performance, and their hierarchal order in the contribution to achieve optimal knee functional performance based on r values. It is clear from Figure 5.1 that the objective measure of quadriceps strength was the most predictive measure for knee function [r= 0.85] (Liu-Ambrose et al. 2003). The latter study is consistent with the results of Wojtys and Huston (2000) that used multiple linear regression analysis for predicting determinants of subjective knee functional capability. The results had shown that quadriceps strength was the most predictive measure followed by hamstrings strengths as second most predictor for subjective knee functional performance even though this study had not offered r values to determine the r values of the two measures described. Figure 5.1 also shows that proprioception was third best predictor based on the study of Borsa et al. (1997) [r=-0.56]. On the other hand, the subjective measure of IKDC was the most predictive measure [r showing significant correlation but not reported] (Sernert et al. 1999) followed by KOOS [r^2=0.15] (Hurd et al. 2008). It is clear from the two Figures 5.1 that most correlations are of weak to moderate relationship between the knee measures (both objective and subjective) and knee functional performance.

5.1.2 Aims of the study

Disassociation among objective as well as subjective measures of capability that could establish or relate to functional performance could be hypothesised to incite sub-optimal conditioning within rehabilitation therapy with the mismatching of perception and objectivity resulting in the underestimation or overestimation by patients of sense of endeavour and the amount of exercise with compromised results. For example, the research by Logertedt et al. (2012) stated that the lower knee function founded on patient-reported measures following ACLR had been related to minimal patient satisfaction and the apprehension concerning re-injury. If comparatively reduced extents of relation are established linking self-perceived and objective measures of function and capability, the issue of the utility of employing one or both of the techniques in the assessment of treatment development becomes more of a challenge. It could additionally infer that the difference in scores related to contrasts in between subjective and objective measures of knee function are established by aspects different to those that are general to both techniques of measurement.

These matters underlie the objectives of the current study which are as follow:

1) To measure correlates of a chosen variety of indices (measures) related to functional and objective neuromuscular outcome measures.
2) To investigate the hierarchy of outcome measures that might determine knee functional performance after ACLR surgery.
3) To investigate whether early change of scores of indices of knee performance predict late change of scores.
4) To investigate the influence of anthropometrics and orthopaedic-related factors on the outcomes of knee function following ACLR surgery and rehabilitation.

Table 5.1: A summary of the studies reviewed in the literature on the relationship between objective and subjective knee measures following ACLR surgery and rehabilitation.

Study	**Between (variables)**	**Results**	**r (pearson correlation coefficient)**	**Pedro score (level of evidence)**	**Conclusion**
Kocher et al. 2004	Knee laxity and IKDC (symptoms, function)	No correlation	r values not reported	Retrospective	Weak correlation between them
Kocher et al. 2002	Patient satisfaction & subjective function	[a]Sig. correlation	r values not reported	Cohort (2)	Subjective satisfaction correlated with IKDC and Lyhsolm
Lavoie et al. 2001	Patient satisfaction (KOOS) & laxity	No correlation	r values not reported	Cohort (2)	KOOS & laxity (pivot shift, lachman)
Wojtys and Huston 2000	Muscle strength and function	[a]Sig. correlation	r values not reported	Cohort (2)	Hamstring 1st, quadriceps 2nd, laxity last as best predictors of function
Liu-Ambrose et al. 2003	Quadriceps and function	[a]Sig. correlation	0.85	RCT (Pedro 7/10)	Quads was determinant of functional ability
Logerstedt et al. 2012	Hop and IKDC	[a]Sig. correlation	OR= (1.09, 1.10)	Cohort (2)	Hop was predictive of self-reported knee function (IKDC)
Hurd et al. 2008	Knee laxity and function (hop)	No correlation	$r^2 = 0.01$	Cohort (1)	Knee laxity did not correlate with function
	Quadriceps and function	Weak	$r^2 = 0.08$		Quads strength had weak correlation with hop

Table 5.1: A summary of the studies reviewed in the literature on the relationship between objective and subjective knee measures following ACLR surgery and rehabilitation.

		correlation			(function)
	Hop and KOOS (function)	Weak correlation	$r^2 = 0.15$		Hop had weak correlation with KOOS (function)
Sernert et al. 1999	Objective and subjective measures	[a]Sig. correlation		Cohort (2)	IKDC and single hop
	IKDC and Lysholm	[a]Sig. correlation	$r = 0.66$		Highest r between IKDC and the Lysholm
	IKDC and laxity	Weak correlation	$r = 0.34$		
	IKDC and hop	Weak correlation	$r = 0.28$		
	Laxity and hop	No correlation	$r = 0.08$		
Snyder-Mackler et al. 1997	Laxity and function (IKDC and Lysholm)	No correlation		Cohort (2)	Laxity measures did not correlate with subjective functional measures

Keys: r^2= coefficient of determination IKDC: International Knee Documentation Committee OR: odd ration

[a]Significant at $p < 0.05$

Figure 5.1: A summary of the studies reviewed in the literature on the relationship (hierarchal order) between knee functional measures (as determined by hop test and patient-reported measures) and both objective and subjective knee measures following ACLR surgery and rehabilitation.

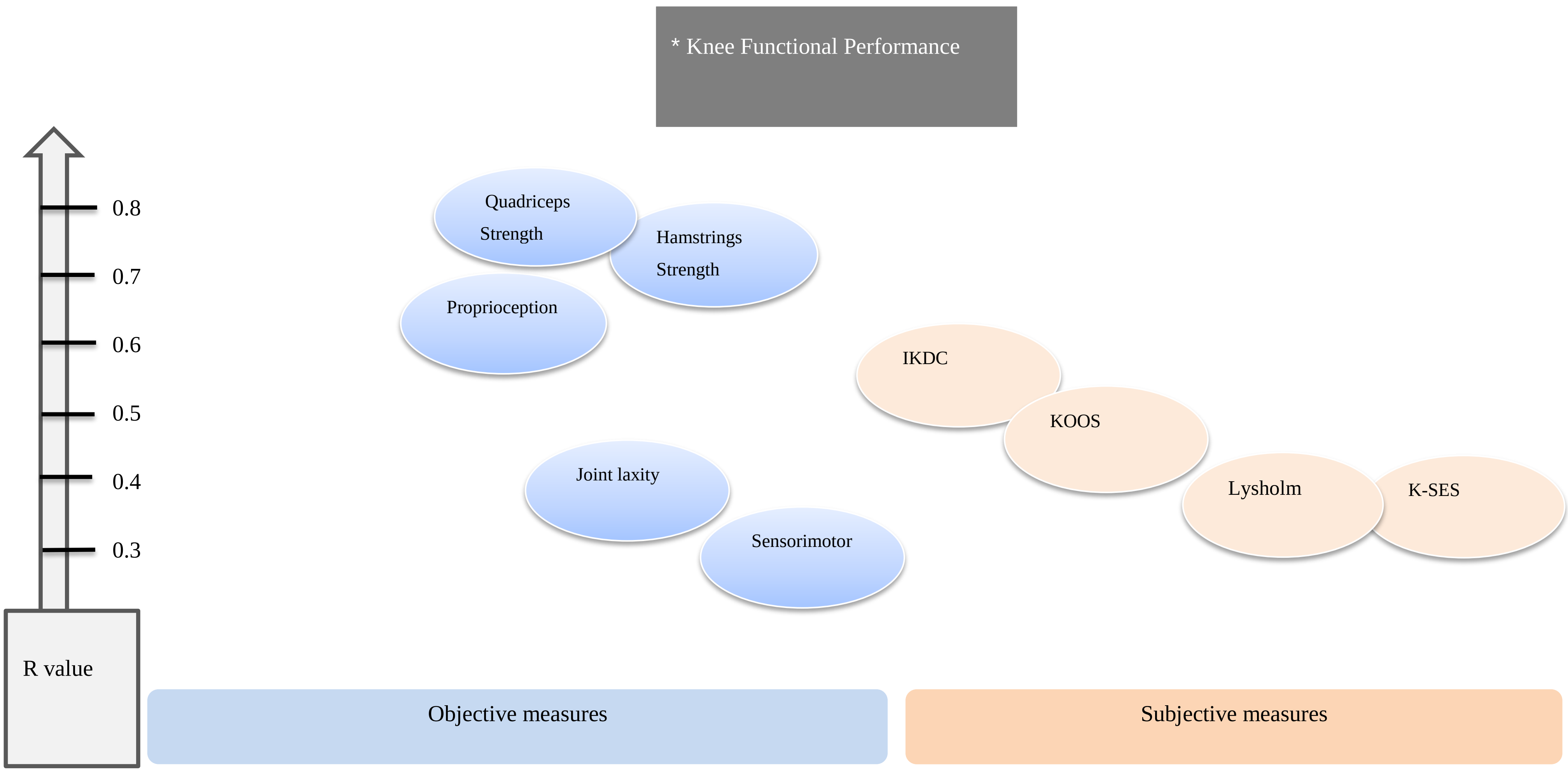
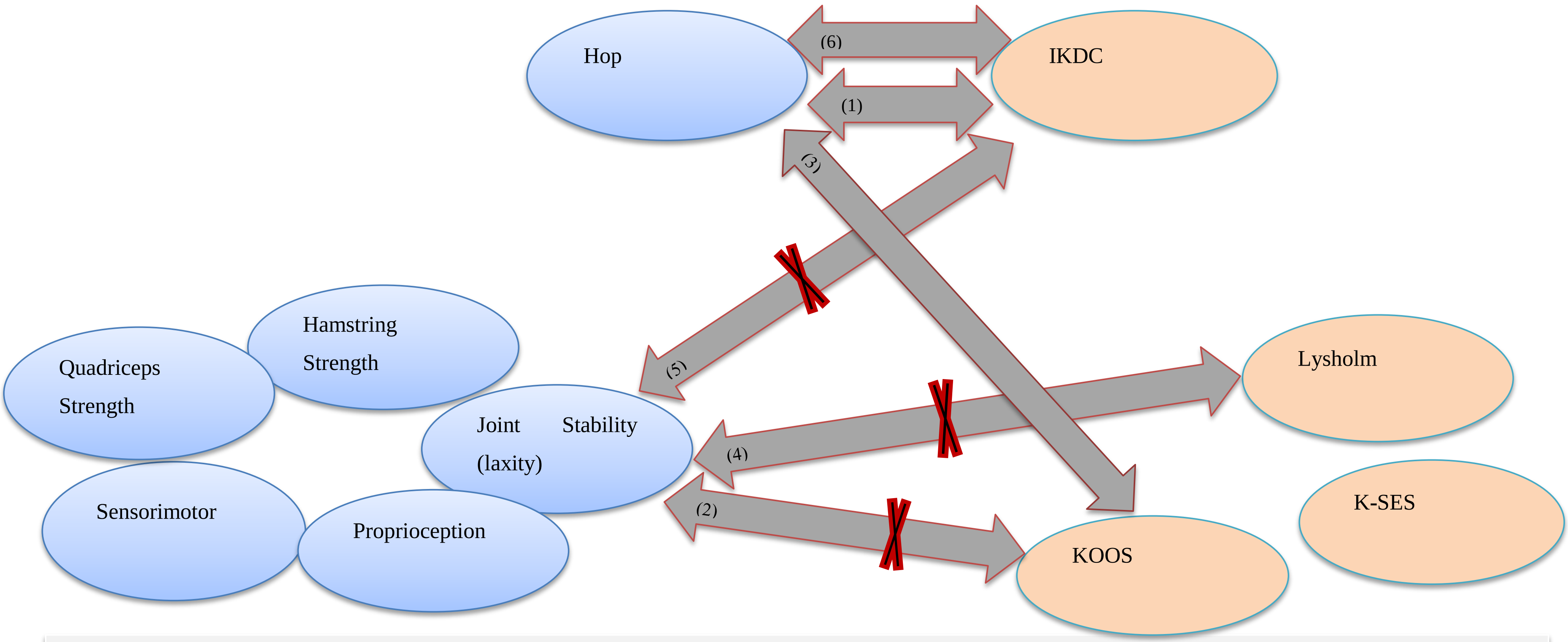


Figure 5.2: A summary of the findings on the relationship between the absolute scores of objective neuromuscular and subjective measures at the end point (24 weeks post-surgery).



(1) Logerstedt et al. 2012	Significant correlation
(2) Lavoie et al. 2001	No correlation
(3) Hurd et al. 2008	Weak correlation
(4) Snyder-Mackler et al. 1997	No correlation
(5) Sernert et al. 1999	No correlation
(6) Sernert et al. 1999	Weak correlation

Numbers given to the arrows refer to the study reviewed

denotes no correlation found

5.2 Method

Participants were part of a randomised control trial within this thesis (chapter four) and had been allocated randomly to two modes of ACLR rehabilitation conditioning and matched in all aspects of delivery with the exception of a systematic manipulation of the sequencing of the patient's exposure to accelerated conditioning programme (further details are presented in method section of chapter three which offered both RJAH contemporary and accelerated rehabilitation guides following ACLR surgery). Forty adults, males, 35 and women, 5 [age (years); mean ± SD,31.58 ± 12.11, height (cm) 174.75 ± 6.67, body mass (kg) 78.25 ± 10.85] were randomly chosen from inside a successive series of patients who underwent ACL reconstructive surgery at U.K National Health Service Foundation Trust Hospital (Robert Jones and Agnes Hunt Hospital). Precise data concerning the undertaking was provided and informed consent was acquired from participants. Prior to recruitment, all patients were assessed using the inclusion and exclusion criteria that have been clarified in the 'methods' section of chapter four. All patients were treated involving four consultant orthopaedic surgeons employing comparable surgical processes and having comparable skills. Participants were advised not to take part in demanding exercise schemes for a minimum of 24 hours before the testing occasions. All patients were tested four times (pre-surgery, 6^{th}, 12^{th} and 24^{th} week following ACLR surgery) on objective and patient-reported outcome measures. A specific outline of the manner of appraisal of these patients on the objective neuromuscular measures has been detailed in the method chapter four of this thesis. The current study had met the ethical standards suggested by Harriss and Atkinson (2009). It was also approved by the Shropshire area NHS Ethics Committee as well as the scientific merit approval from the Research Committee of Robert Jones and Agnes Hunt Orthopaedic and District Hospital Foundation NHS Trust, UK.

5.2.1 Experimental and assessment procedures

Because the current study is part of a previous RCT study within this thesis (chapter four), the reader is therefore advised to refer to the methods section of the latter chapter for full details of the experimental and assessment tools and procedures of this trial.

5.2.2 Statistical Analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS, version 20.0 for windows). Pearson product-moment correlation coefficient was computed to declare association amongst subjective (patient-reported outcomes) and objective measures employed to assess knee functional performance in four testing occasions (pre-surgery, 06, 12 and 24 week post ACLR surgery). The Pearson product-moment correlation coefficient comprises a quantification of the power of a linear relation between two variables (Pearson's correlation coefficient). It is quantified on a scale that has no units and may embody a value from +1 to -1, in which +1 signifies likely strong positive correlation, while -1 signifies likely strong negative association, and 0 signifies no relation between the variables. The power of association is usually declared as minimal or reduced correlation comprising r=0.1-0.29, medium correlation comprising r=0.3 -0.49 and great or high comprising ≥ 0.5. In addition, where possible, coefficient of determination (r^2) was used and calculated to predict the future outcomes of indices employed in this study.

5.3 Results

5.3.1 Correlation between objective functional and subjective functional measures

The results here represent the absolute scores of injured legs at pre-surgery (0 weeks), 12 and 24 weeks post-surgery. Because single leg hop, KOOS, K-SES, Lysholm and IKDC were used to determine the knee function (primary outcomes of the study), it is worth investigating first the correlation between the latter primary outcome measures.

	Hop (injured)			Hop (uninjured)		
	pre-	12 weeks	24 weeks	pre-	12 weeks	24 weeks
IKDC (pre-)						
IKDC 12 weeks						
IKDC 24 weeks						
K-SES [PA] (pre-)						
K-SES [PA] 12 weeks		0.38*				
K-SES [PA] 24 weeks						
KOOS [P] (pre-)						
KOOS [P] 12 weeks		0.35**				
KOOS [P] 24 weeks						
Lysholm (pre-)						
Lysholm 12 weeks		0.32**				
Lysholm 24 weeks						

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed)

Key: PA; physical activity, P: pain.

Table 5.2: Relationships between the absolute scores of the functional outcome measures (subjective and objective measures) at pre-surgery, 12 and 24 weeks post-surgery.

Table 5.2 suggests there were small to moderate correlations between the objective functional measures (single leg hop) and subjective functional measures (IKDC, KOOS, K-SES, Lysholm) at 12 weeks post-surgery. Because the pattern of non-significant and poor correlation was observed in the uninjured legs in all the correlation tests, a decision had been taken to present tables of measures that demonstrated significant correlation only.

Table 5.3: A summary of the finding of absolute scores between the objective and subjective measures of knee function at 12 weeks post-surgery (the period corresponded to highest correlation found during the ACLR rehabilitation).

5.3.2 Correlation between functional measures and objective measures

	Peak force			RFD			SMP		ATFD (injured)
	Quad (injured)		Hams (injured)	Quad (injured)		Hams (injured)	Quad (injured)	Hams (injured)	
	pre-	12 weeks	12 weeks	pre-	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
Lysholm (pre-)									
KOOS [P] (pre-)	-.43*								
KOOS [QOL] (pre-)				-.43*					
Lysholm 12 weeks			.32*						
KOOS [P] 12 weeks		-.34*					-.46**	.45**	-.32*
KOOS [QOL] 12 weeks									
K-SES 12						.42*		.44*	
IKDC 12 weeks									
Hop injured 12 weeks			0.42*						
Lysholm 24 weeks									
KOOS [P] 24 weeks					-.31*				
KOOS [QOL] 24 weeks									
K-SES 24 weeks									
IKDC 24 weeks									

Key: P; pain, PA; physical activity.

Table 5.3 suggests there was a more prominent correlation between the absolute scores of functional measures (objective [single leg hop] and subjective [IKDC, KOOS, K-SES, Lysholm) and the objective neuromuscular measures (peak forces, EMD, RFD, SMP of quadriceps and hamstrings) mainly at 12 weeks post-surgery.

5.3.3 Correlation between objective functional and subjective functional (change scores)

As well as analysing the absolute scores at all test occasions (i.e at pre-surgery, 12, 24 weeks post-surgery), the aim of the current study was also to assess the change scores of measures (i.e at pre-surgery to 12 and 12 to 24 weeks post-surgery) in order to investigate the clinical efficacy of accelerated conditioning at the early and late phases of ACLR rehabilitation.

	Hop (injured)	
	pre-12 weeks	12-24 weeks
IKDC (pre-12 weeks)	0.43*	
IKDC 12-24 weeks		
K-SES [PA] (pre-12 weeks)		0.32*
K-SES [PA] 12-24weeks		
KOOS [P] (pre-12 weeks)	0.35*	
KOOS [P] 12-24 weeks		
KOOS [QOL] (pre-12 weeks)		
KOOS [QOL] (12-24 weeks)	0.32*	
Lysholm (pre-12 weeks)	0.46**	
Lysholm 12-24 weeks		

Key: PA; physical activity, P; pain, QOL; quality of life

Table 5.4: Relationships between the change scores of the objective functional and subjective functional outcome measures at pre-surgery to 12 and 12 to 24 weeks post-surgery.

5.3.4 Correlation between functional measures and objective measures (change scores)

		Peak force (Quad injured)		RFD (Quad injured)	EMD (Hams injured)	EMD (Quad injured)	SMP (Quad injured)
		pre-12 weeks	12-24	pre-12 weeks	pre-12 weeks	pre-12 weeks	pre-12 weeks
Hop (injured)	pre-12 weeks	0.35*		0.33*			
	12-24 weeks						
IKDC	pre-12 weeks	0.32*		0.37*	0.34*		
	12-24 weeks		0.35*				
K-SES (DA)	pre-12 weeks						
	12-24 weeks				0.33*		
KOOS (PA)	pre-12 weeks						0.47**
	12-24 weeks						
Lysholm	pre-12 weeks					0.42**	
	12-24 weeks						

Table 5.5: Relationships between the change scores of the functional outcome measures (subjective and objective measures) and objective neuromuscular at pre-surgery to 12 and 12 to 24 weeks post-surgery. Key: DA; daily activity, PA; physical activity.

5.3.5 Early change of scores versus late change of scores

Objective measures

		Hop (injured) 12-24 weeks	Peak force (Quad injured) 12-24 weeks	EMD (Hams injured) 12-24 weeks	RFD (Hams injured) 12-24 weeks
Hop (injured)	pre- 12 weeks	-.75**			
Peak force (Quad injured)	pre-12 weeks		-.62**		
RFD (Quad injured)	pre- 12 weeks			.36*	
EMD (Hams injured)	pre-12 weeks				.42*

Table 5.6: Relationships between the early and late change scores over time in objective outcomes at pre- to 12 and 12 to 24 weeks post-surgery.

Table 5.6 suggests that there were strong negative relationships between the early and late change scores of functional objective measure (single leg hop) and early and late change scores of objective measure (peak force of quadriceps) while there were small relationship between early and late change scores of RFD (quadriceps) and EMD (hamstrings) during ACLR rehabilitation.

Subjective measures

		KOOS (P) 12-24	KOOS (QOL) 12-24	Lysholm 12-24	IKDC 12- 24
KOOS (P)	pre-12 weeks	-.33*			
KOOS (QOL)	pre-12 weeks		-.40*		
Lysholm	pre-12 weeks			-.33*	
IKDC	Pre-12 weeks				-0.15

Table 5.7: Relationships between early and late change scores in the subjective measures of Lysholm, KOOS (pain) and KOOS (quality of life) during the period pre- to 12 and 12 to 24 weeks post-surgery.

Table 5.7 suggests that there were small negative relationship between early and late change scores of functional subjective measures (KOOS [quality of life and pain], Lysholm) while there was no relationship between early and late change scores of IKDC (not presented in the table) during ACLR rehabilitation.

5.3.6 Anthropometrics and orthopaedic-related relevant factors

Unstructured physical activity and functional objective measure

The results here represent the change scores of injured/uninjured legs of single leg hop at pre- to 12 and 12 to 24 weeks postoperatively.

		Hop (injured)	Hop (uninjured)	Hop (injured)	Hop (uninjured)
		pre- 12 weeks	pre- 12 weeks	12 to 24 weeks	12 to 24 weeks
Unstructured physical activity	pre- 12 weeks	.33*	0.01	0.01	-0.3
Unstructured physical activity	12 to 24 weeks	0.06	-0.18	-0.01	0.27

Table 5.8: Relationship between unstructured physical activity and functional objective measure (single leg hop)

Unstructured physical activity and objective measure

		Peak force (Quad injured)	
		pre- 12 weeks	12 to 24 weeks
Unstructured physical acitvity	pre- 12 weeks	0.25	-0.22
Unstructured physical acitvity	12 to 24 weeks	0.12	-01.2

Table 5.9: Relationship between unstructured physical activity and objective measure (peak force of quadriceps).

Table 5.8 and 5.9 suggest poor correlation between unstructured physical activity and functional outcome measure of single leg hop and objective measure (peak force of quadriceps).This pattern of non-significant correlation was also observed between the orthopaedic-related factors of body mass and waiting time to surgery and all the outcome measures of the knee function.

Figure 5.3: A relationship between the absolute scores of objective and subjective measures of knee function at 12 weeks post-surgery (corresponding to a period of highest correlation found in the study).

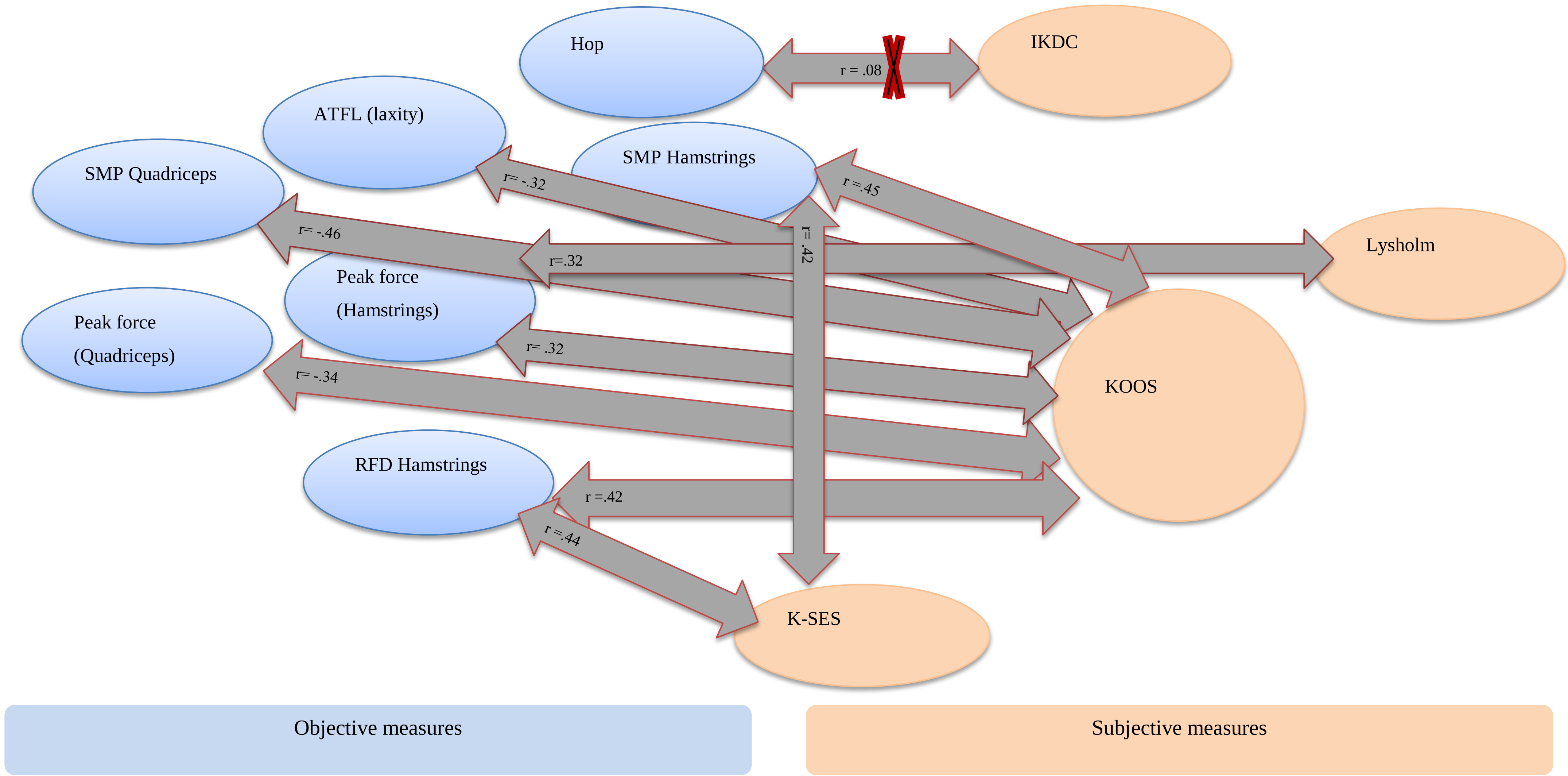


Figure 5.4: A summary of the findings illustrating the relationship between the change scores of objective (injured legs) and subjective measures in determining knee function at pre-surgery and 12 weeks post-surgery during ACLR rehabilitation.

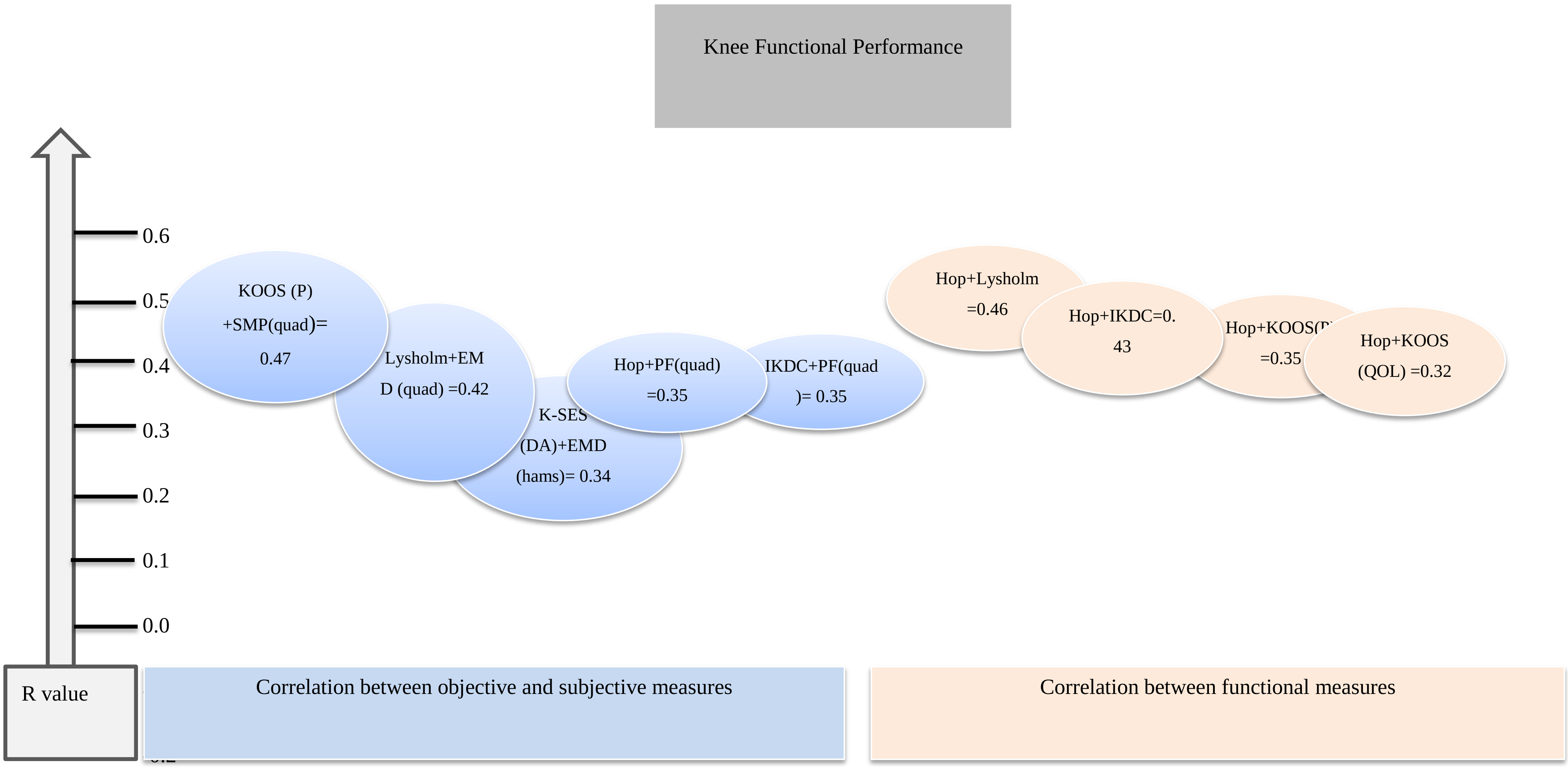
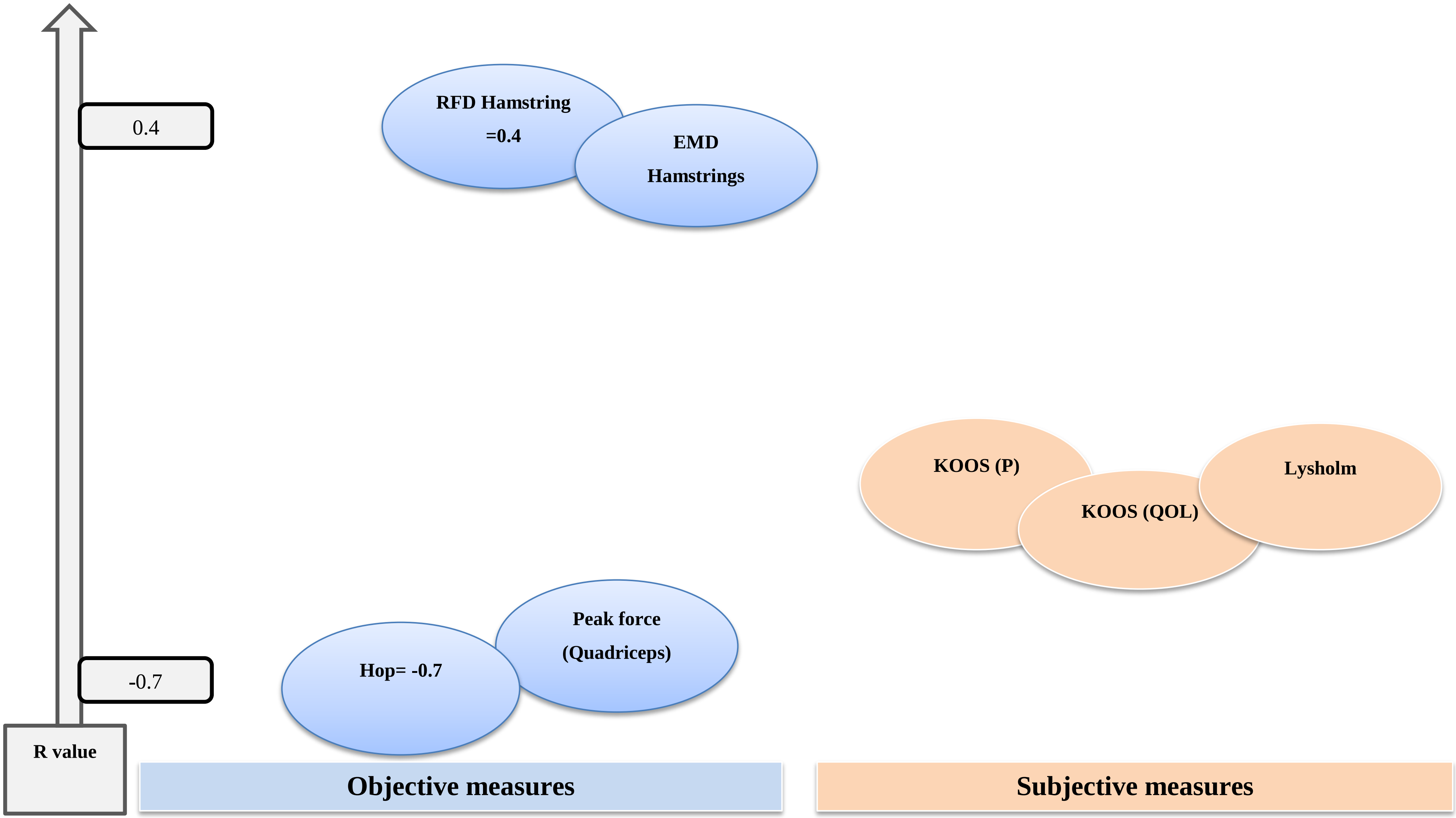


Figure 5.5: A summary of the findings on the relationship between the early change scores (pre-surgery to 12 weeks post-surgery) and late (12 to 24 weeks post-surgery) during ACLR rehabilitation. For instance it is evident from the diagram that RFD of hamstrings had the highest correlation between early and late change scores while single leg hop test had the highest negative correlation between the latter change scores.



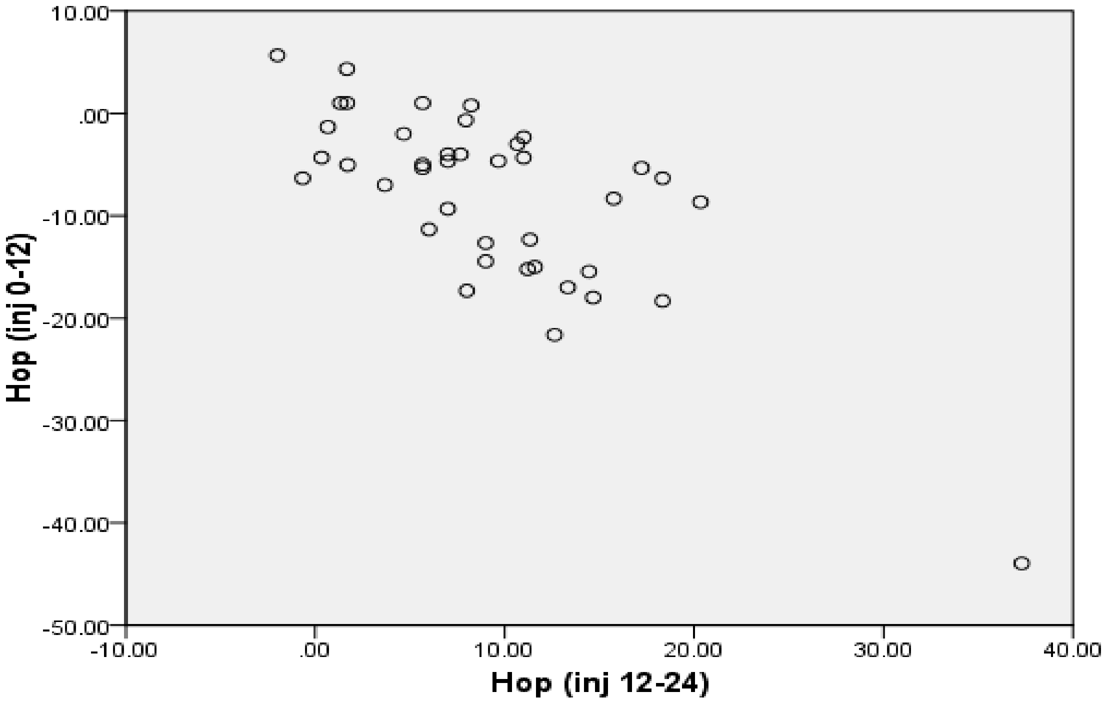


Figure 5.10: A graph showing the negative relationship between the early change score and late change scores of a single leg hop performance (injured legs) following ACLR rehabilitation. The graph implies that the mean change scores in the early phase (pre-surgery (0) to 12 weeks post-surgery) of ACLR rehabilitation was negatively correlated (r= -0.75) with the mean change scores in the late phase (12 to 24 weeks post-surgery) of rehabilitation.

5.4 Discussion

This discussion will be divided into four main sub-sections that reflect the aims of this current study: 1) the correlations between objective and subjective outcome measures, 2) the hierarchy of objective and subjective measures for determining knee functional performance 3) does the early change scores of knee outcome measure predict late change scores and 4) anthropometrics and orthopaedic related factors influencing knee functional performance.

5.4.1 Correlation between objective and subjective measures

Objective functional and subjective functional measures

When the absolute scores of measures at each testing occasion (pre-surgery, 12 and 24 weeks post-surgery) were analysed, the results of the current study showed small correlations between the objective functional measure (single leg hop for the injured leg) and the subjective functional measures (KOOS, K-SES, Lysholm, IKDC) [r=0.38 with K-SES (PA), 0.35 with KOOS (P), 0.32 with Lysholm, and 0.12 with IKDC, p>0.05] at 12 week post-surgery. This finding is similar to those previously reported in the study of Sernert et al. (1999) who also did not show any correlation between IKDC and the single leg hop measures. Hurd et al. (2008) also reported a weak correlation between KOOS and the hop test (r^2=0.15). The results of the current study might have an important implication on the approaches used by clinicians as well as therapists in determining the progress of ACLR rehabilitation. Determining the progress of ACLR rehabilitation should be based on a patient’s physical neuromuscular capabilities (objective measure) as well as the patient’s perception about their progress (subjective measure) and any mismatch between these two measures might result in poor rehabilitation planning as both measures are expected to assess the same capability. Therefore if one measure is selected over the other then an unjustifiable bias might be introduced in the process of progress during ACLR rehabilitation (Ardern et al. 2011). However, the work of Logerstedt et al. (2012) found a significant correlation between hop tests and subjective knee function using IKDC during the period between 6 months and one year after ACLR surgery. The latter study indicated that the assessment of a hop test in the late phase of rehabilitation (i.e after 6 months following ACLR surgery) could offer a better and more appropriate prediction of the status of knee function on the basis of there being a matching between the objective and the subjective measures. This might have an implication for clinicians as well as therapists in terms of making better use and in the interpretation of hop tests in the late stages of ACLR rehabilitation rather than the acute stages. Despite this, clinicians must interpret the study results of Logerstedt et al. (2012) with caution as the number of patients who completed the 6 months to one year hop tests was small while the study only included an actively young population, making it impossible to generalise the results to other age groups.

Objective and subjective measures (absolute scores at 12 and 24 weeks post-surgery)

When the absolute scores of measures were analysed at 12 weeks post-surgery, there were generally small to moderate correlations between the objective neuromuscular and the subjective patient-reported outcome measures in the current study [r ranged between -.31 to -.46] (Figure 5.3). KOOS (pain and quality of life sub-sections) had shown the most consistent correlation at 12 weeks post-surgery with objective measures of SMP for quadriceps [injured leg]; -0.46, $p<0.01$, peak force of quadriceps [injured leg]; -0.34, $p<0.05$, ATFD [injured leg]; -0.32, $p<0.01$. The negative relationships suggest that while the rate of change of the latter outcome measures had shown improvement in the subjective measure (KOOS pain and quality of life), there was a lack of improvement in the objective measures (SMP for quadriceps, peak force and ATFD) at 12 weeks post-surgery. On the other hand, when the absolute scores of measures were analysed at the end point (24 weeks post-surgery) of ACLR rehabilitation, there were generally no correlations ($p>0.05$) between the objective neuromuscular and subjective patient-reported outcome measures in the current study. Interestingly the results had also shown lack of relationship between the objective functional (single leg hop) and the subjective functional measures (IKDC, KOOS, K-SES, Lysholm). This mismatching between what patients perceived about their knee function and the objective neuromuscular measures might indicate the possibility that each measure had assessed independently different aspects of knee function. The heterogeneity in the level correlation (small, moderate and lack of correlation) amongst patient-reported outcome measures in the current study might imply that each outcome measure of function (objective single leg hop and patient-reported outcome measures) might have a separate individual contribution in determining the important aspects of knee functional capability following ACLR surgery and the subsequent rehabilitation.

Although the correlations were small to moderate as well as negative, the possible explanation for this relationship between the absolute scores of KOOS (pain and quality of life domains) might be due to the advantage of KOOS in separating the scores of each domain thus allowing for a better understanding of the contribution of each domain in the subjective evaluation of knee functional capabilities. While KOOS had shown more correlation with objective measures than other patient-reported outcome measures, the absolute scores of K-SES and Lysholm shared the second position in terms of the hierarchy of the relationship with objective measures. K-SES had shown moderate correlation with RFD of hamstrings [injured leg]; 0.44 and SMP of hamstrings [injured leg]; 0.42, $p<0.05$, while Lysholm had shown moderate correlation with measures of SMP for hamstrings [injured leg]; 0.45, $p<0.01$ and a small correlation with the peak force of hamstrings [injured leg]; 0.32, $p<0.05$. It seems that hamstrings rather than quadriceps that appeared to show positive correlation with subjective measures of K-SES and Lyhsolm, suggesting that although the majority of participants in the current study had a hamstring graft, the individual perception towards their hamstring muscular performance was not affected by the type of surgery performed. In addition, no correlation was found between IKDC and objective measures of knee function. With regards to knee laxity, apart from the small relationship with KOOS (P), there was an absence of association between knee laxity (ATFD) and objective and subjective measures. This might be endorsed by the study of Wojtys and Huston (2000) who reported that following six months of ACLR rehabilitation, the knee laxity of the operated side was similar in terms of tightness to the contralateral side (6.1 versus 6.2 mm, respectively). The possible mechanism underpinning this would be that lack of variability does not provoke any possibility for correlation. The latter authors suggested that in order to conduct a more meaningful assessment of the knee laxity test, obtaining further tests beyond six months of ACLR rehabilitation was advised for the injured knee.

A priori expectations for the change scores of objective versus subjective measures in the current study was to observe positive correlations over time amongst the latter measures. For instance, single leg hop (objective), IKDC and Lyhsolm (subjective patient-reported measures) have been extensively used in the literature to essentially measure knee function (Logerstedt et al. 2012, Sernert et al. 1999), thus positive correlation would be expected amongst the latter three measures. Similarly, SMP, EMD and RFD [essential components of knee functional tasks that regulate reaction time (EMD), force generation (RFD) and muscle re-education following injury disruption (SMP)] had not shown correlation amongst them, implying that each of the latter measures might have an independently separate contribution and role in underpinning the important aspects of knee capability. Relationships amongst the latter outcome measures (functional and objective neuromuscular) had not been frequently observed in the current study. In addition, altered variability (heterogeneity within the sample) due to the systematic intervention introduced (accelerated conditioning) in the current study might possibly have facilitated increased correlation in the acute and sub-acute phases of ACLR rehabilitation, but worked against the ‘aim’ of achieving more consistent outcomes at the end of rehabilitation for patients.

5.4.2 Hierarchy of objective and subjective measures for determining knee functional performance

As mentioned earlier in the aims of this study, the change scores of the objective and subjective measures (i.e from pre-surgery to 12 and 12 to 24 weeks post-surgery) were investigated to examine the clinical efficacy of accelerated conditioning both in the period of accelerated intervention (up to 12 weeks post-surgery) and the late phase of ACLR rehabilitation. When the pattern of change scores between pre-surgery to 12 weeks post-surgery was analysed, the highest correlation (moderate correlations) were observed between KOOS and SMP (0.47), hop and Lysholm (0.46), hop (injured legs) and IKDC (0.43) and Lysholm and EMD (quadriceps of the injured leg). As mentioned earlier, the expectation in the current study was, for all outcome measures that have been purported to be valid estimates of function, to be appropriately correlated at any given moment of assessment (whether it be pre-surgery, or at regular assessment occasions afterwards (6, 12 and 24 weeks post-surgery). It was also expected that the extent of changes in the latter outcomes over given periods of time (i.e. responsiveness) should be 'congruent'. However the small correlations observed in the current study seem to be clinically compromised (coefficient of determination [r^2=0.08) suggesting that meaningful prediction models amongst early post-surgery changes in objectively-measured and patient-reported outcomes of function would not be feasible statistically. Moreover, the study of Hurd et al. (2008) was consistent with the current finding as the latter found relatively weak correlation between the objective (single leg hop) and subjective (KOOS) measure [r^2=0.15]. Although all the study measures had shown small to moderate correlations amongst them, it was interesting to observe that no correlation was found between ATFD and any other objective or subjective measures of knee function. The data in the current study further supports the notion that knee laxity assessment at 6 months follow up does not inform about the knee functional status (Wojtys and Huston 2000).

In addition, quadriceps (injured leg) musculature had shown more consistent correlation (small to moderate) than hamstrings. For instance, weak to moderate correlations between the change scores of EMD and peak force of quadriceps, and the functional measures of Lysholm, hop and IKDC (0.42, 0.35, and 0.32, $p<0.05$, respectively) were observed at pre-surgery to 12 weeks post-surgery. Although the current study is consistent with the findings of Liu-Ambrose et al. (2003) that suggested the peak force of quadriceps was predictive of knee functional performance (r=0.85), the correlation observed between the change scores of peak force for quadriceps and the functional measures in the current study were relatively weak (ranged from 0.35 to 0.42). As such these correlations cannot be utilised to predict the knee function following ACLR rehabilitation. On the other hand, RFD and EMD of hamstrings and quadriceps were expected to show prominent correlation with subjective measures as the latter indices (EMD and RFD) are necessary neuromuscular factors that are required for generating functional movements such as hopping. However, the current study had shown small to moderate correlation between the change scores of EMD and Lysholm and K-SES (0.42 and 0.34, $p<0.05$, respectively). These findings further ignite the important debate over the clinimetric utility of patient-reported outcome measures since patient-perceptions of capability are mis-scaled against a variety of objectively-measured outcomes of function and neuromuscular performance. The latter imply that the capability of patients to self-manage rehabilitation (e.g. government directives) effectively and efficiently would be compromised if progress is only monitored by patient-reported outcome measures.

5.4.3 Does early change score predict late change score?

Although there were negatively small correlations between the early (pre-surgery to12 weeks post-surgery) and late (12 to 24 weeks post-surgery) change scores for the subjective measures [IKDC; -0.24, KOOS (pain);-0.33, KOOS (quality of life); -0.40, Lysholm; -0.33, $p<0.05$], the most interesting finding was the large negative relationship between the early and late change scores of single leg hop (injured legs) [$r=-0.75$, $p<0.01$] (Figure 5.5). The negative relationships suggest that while the rate of change (responsiveness) of the latter outcome measures had shown improvement in single leg hop performance in the early stage (pre-surgery-12 weeks post-surgery) of rehabilitation, there was a lack of improvement in the latter's performance in the late stage of rehabilitation (12-24 weeks post-surgery). This indicates that those improving most (0-12) showed worst improvements (12-24); physiological 'ceiling' effects. Given that heterogeneity was introduced systematically for the accelerated group, the possible explanation for the negative relationships observed between the early and late change scores of measures was that they were affected by the improvement of the objective and subjective measures in the first 12 weeks due to the intervention of accelerated conditioning of ACLR rehabilitation. However, the data had been "pooled" (accelerated and contemporary groups) in the current study to permit correlations amongst a bigger sample. Therefore, it would be difficult to use the latter explanation as a justification for the 'negative' relationship observed. However, given that single leg hop was the primary objective functional outcome measure for this study, the possible clinical implication for the negative relationship suggests the fact that clinicians should not rely on one measure (be it objective or subjective) for determining the readiness to resume normal physical activities and indeed the optimal functional performance of the knee.

Another negative correlation observed in the current study was between the early and late change scores for quadriceps peak forces (injured legs) [-0.62, $p<0.01$], suggesting that while the rate of change (responsiveness) of the peak forces for the quadriceps had shown improvement in the early stage (pre-surgery-12 weeks post-surgery) of ACLR rehabilitation, there was a lack of improvement in the latter muscle strength in the late stage of rehabilitation (12- 24 weeks post-surgery). This might suggest that those improving most (0-12) showed worst improvements (12-24) that could be attributed to physiological 'ceiling' effects. To the knowledge of the author of this research, no previous study had reported negative relationship between the early and late change scores of the outcome measure of peak force for quadriceps. In contrast, small to moderate correlation were found between the early and late change scores of RFD and EMD for hamstrings (injured legs) [r= 0.36, 0.42, $p<0.05$, respectively]. Given that EMD and RFD are important components that regulate the reaction time and generation of force of the knee joint (Gleeson et al. 2009), the current findings indicate that the latter components had not been compromised amongst patients of hamstrings grafts (representing 92% of the sample). However, the magnitudes of correlation (early versus late change scores of RFD and EMD for hamstrings) are still considered to be clinically compromised ($r < 0.7$) in terms of justifying the use of accelerated intervention and subsequently the change in practice for ACLR rehabilitation. On the other hand, it was surprising that despite the design of the repeated-measures of the current study, the lack of correlation in the indices of ATFD and SMP that had shown 'no' correlation implying that the early responses of patients (response to the 'intervention' phases in the contemporary or accelerated groups) were not related to later dose-responses. With regards to knee laxity, it seems in the study of Wojtys and Huston (2000), who reported similarities in tightness (decreased anterior tibio-femoral displacement) between the injured knee and the contralateral side, that the assessment of ATFD beyond six months after ACLR surgery could provide a more meaningful assessment of the ATFD test that might inform the clinical efficacy of the latter measure during ACLR rehabilitation. In addition, Beynnon et al. (2011) reported a similarity in increased knee laxity (anterior-posterior displacement of the tibia relative to the femur) at two years follow up in both the accelerated and non-accelerated rehabilitation groups (3.2 versus 4.5 mm, respectively, $p>0.05$) following ACLR surgery. It is also plausible that in the current study the similarity of laxity perhaps implies a similarity in population variance for both groups (accelerated and contemporary) and therefore, limited variance to influence correlation.

5.4.4 Anthropometrics and orthopaedic-related factors influencing knee function following ACLR surgery and rehabilitation

As mentioned in chapter four (study one), when controlling for orthopaedic-related factors such as waiting time, and unstructured physical activity and body mass, significant interaction responses (group by time by leg) had been observed in some outcome measures of function and objective neuromuscular capability over the time-course of formal rehabilitation indicating that the latter factors had an influence on the outcomes of ACLR rehabilitation. As such, the author of this thesis decided to further investigate the relative influence of the latter factors by assessing the extent and robustness of the relationship between the change scores of the 'orthopaedically-related factors' such as unstructured physical activity, body mass and waiting time, and the change scores associated with objectively-measured and patient-reported (subjective) outcomes.

A significant correlation between pre-surgery to 12 week post-surgery was observed between the unstructured physical activity and single leg hop [injured leg] ($r=0.33$, $p<0.05$). No other significant correlation was observed between the change scores of unstructured physical activity and subjective functional or objective neuromuscular capabilities. However, the small correlation observed between the unstructured physical activity and single leg hop might clinically implies that unstructured physical activity had indeed an influence on the objective primary outcome of knee function (single leg hop) but not clinically strong enough to predict true and meaningful changes.

5.4.5 Clinical implications and conclusion

One important finding of this study was the lack of significant association between the objective and subjective measures particularly between the objective functional and subjective functional measures (single leg hop, KOOS, K-SES, Lysholm and IKDC). It is therefore plausible that the functional objective measure does not necessarily reflect what patients perceive about their knee functional condition. Clinicians and therapists should therefore be cautious not to progress and plan their rehabilitative regime based on one sole particular measure. This is so because currently there is no evidence from the literature to suggest an ideal outcome measure that assesses knee function following ACLR surgery and subsequent rehabilitation (Lavoie et al. 2001).

In summary, the relationships amongst the indices (objective and subjective measures) of knee function following ACLR rehabilitation were either small or moderate indicating that these relationships are not statistically strong enough to predict future knee function. The latter correlations are non-existent for a good proportion of the potential relationships investigated. Equally, the data are insufficient to predict which measures are the most important predictors for optimal knee function as the coefficient of determination (r^2) suggested less than 10% of the shared variance between the outcome measures of the study. In addition, large negative correlations were observed in single leg hop (objective functional measure) and peak force for quadriceps (objective neuromuscular measure) suggesting that the rate of change (responsiveness) of the latter outcome measures had shown improvement in the early stage (pre-surgery-12 weeks post-surgery) of rehabilitation, but no improvement in the late stage of rehabilitation (12-24 weeks post-surgery). Lastly, a small correlation had been observed between the unstructured physical activity and single leg hop but this was not clinically strong enough to predict true and meaningful changes. The results of the current study supports the notion that for the purpose of evaluating post-surgical ACLR outcomes, the current practice of ACLR rehabilitation as well as future research should focus on investigating the concurrent use of functional, objective neuromuscular and subjective patient-reported measures.

6 Chapter Six (Study Three)

Influence of ACE I/D Gene Polymorphism on Responsiveness to Rehabilitative Training and the Outcomes of Knee Function Following Anterior Cruciate Ligament Reconstruction

6.1 Introduction

The variability observed amongst individuals due to both genetic differences and the environment under which they develop is referred to as gene-environment interaction (Perusse et al. 2013). There are two approaches in humans to determine genes that explain variations in physical performances; first is the localisation of individual “loci” that make up the components of performance phenotype by Quantitative Trait Loci (QTL) linkage analysis. The QTL refers to phenotypes that vary in degree and can be attributed to polygenic effects (i.e. product of two or more genes) and their environment. The second approach is the allelic (genotypic) association studies in which a specific marker genotype is studied within a candidate gene in groups of different genotypes (Rankinen et al. 2006). Association studies can also take the form of a case control design study in which a comparison, for instance, is made between genotype frequencies of endurance athletes and controls. The case-control design studies incorporate a comparison, for instance, between genotype frequencies of endurance athletes and a control group, whereas cross sectional studies examine, for example, participants with different genotypes on their physical performance phenotypes (Macarthur and North 2005). In comparison to QTL linkage analysis studies, the association studies do not require genetically related subjects (Beunen et al. 2010). An association studies’ approach was used in the research within this chapter as association studies do not require genetically related subjects (i.e. it only requires participants with a well-defined phenotype against a matched normal participants (control) whereas linkage analysis studies require the cooperation of genetically related subjects (Beunen et al. 2010). To the knowledge of the author of this thesis, the study of this chapter would be the first exploratory clinical trial which examined the influence of a candidate gene polymorphism (namely ACE Insertion/Deletion gene polymorphism) on responsiveness to strength training, thus understanding the clinical utility and pragmatism associated with deployment in real-world patient groups.

Phenotype is the characteristic an individual possesses as a result of gene-environment interaction. For a particular phenotype, the variations can still be observed on how an individual can adapt (response) to a stimulus or an environment (phenotype). For example it is very possible to find high responders, average responders and low responders to an endurance exercise phenotype. Gene polymorphism is the presence of two or more forms of allele (genotype) of a single gene that can exist in an individual. Detecting gene polymorphism is often useful in population studies for the purpose of assessing the degree of genetic diversity within a group of people (Rankinen et al. 2010). Several gene polymorphisms have been found to have association with fitness parameters such as strength and endurance (ACE I/D; Pescatello et al. 2006, Charbonneau et al. 2008, ACTN3 R577X; Clarkson et al. 2005, IGF1 CA-repeat ; Sood et al. 2012, rs1024610 polymorphisms of chemokine (C-C motif) ligand 2 (CCL2) and rs768539 of its receptor (CCR2); Harmon et al, 2010).

The ethical approval of the current study was obtained to analyse the candidate gene polymorphisms that are known to be responsive to exercise training, namely ACE I/D and ACTN3 R577X polymorphisms. The latter two genes have become broadly studied candidates with respect to the investigation of responsiveness to exercise conditioning (Colakoglu et al. 2005, Giaccaglia et al. 2008, Delmonico et al. 2007, Norman et al. 2009). In addition, based on the literature (Hand et al. 2007, Gomez-Gallego et al. 2009) responsiveness to exercise training is thought to be due to polygenic effect rather than one single gene. Although there is growing evidence showing that polymorphisms investigated together can potentially increase the power to detect the association of genes in responsiveness to training, majority of studies within the literature were carried out with single allelic variations.

Therefore the initial plan for this thesis was to analyse two gene polymorphisms, namely ACE ID and ACTN3 R577X polymorphisms. However due to limited resources and limited time frame associated with PhD programme, the researcher had to choose one gene polymorphism (namely ACE I/D polymorphism) for the evaluation of effect of gene polymorphism on responsiveness to physical training following ACLR surgery. However, given the fact that responsiveness to physical training is due to polygenic effect, the researcher of this thesis will pursue the analysis of ACTN3 R577X polymorphism in the near future in order to determine the effect of combined two genes (polygenic effect) on responsiveness to physical training.

Angiotensinconverting enzyme (ACE) plays an important role in circulating human renin-angiotensin system. The latter system is a hormonal cascade that regulates the function of cardiovascular system and determines degrading the vasodilator “kinins” and generating the vasoconstrictor “angiotensin II” (Folland et al. 2000). The process begins with renin production which is responsible for the conversion of angiotensin to inactive angiotensin I. The ACE enzyme then transforms the latter angiotensin II, known as an active vasoconstrictor (Pescatello et al. 2006). In addition, Kinins and angiotensin II were found to play a role in the regulation of tissue growth particularly as a regulator of muscular hypertrophy. ACE gene has an insertion (I) and deletion (D) polymorphism (ACE I/D). However, a functional polymorphism of this gene polymorphism is found in the I and not the D allele which has been reported to have high enzyme activity in tissue and serum. Homozygotes for the D allele in particular have been found to have an association with vascular muscle growth located in the coronary angioplasty. Relevant to this thesis, the latter allele has been associated with cardiac hypertrophy in human as a result of exercise training (i.e. dose-response). Because increased ACE activity was found in skeletal muscles, it is plausible that response to exercise training might be influenced by D allele of ACE I/D polymorphism (Charbonneau et al. 2008). As such, this has prompted researchers to investigate the relationship between ACE I/D polymorphism and response of muscle phenotypes to exercise training.

Based on the systematic review (genetic influence on responsiveness to strength training (chapter three), eight studies (Colakoglu et al. 2005, Pescatello et al. 2006, Charbonneau et al. 2008, Giaccaglia et al. 2008, Lima et al. 2011, Folland et al. 2000, Williams et al. 2005, Thomis et al. 2004) had investigated the effects of ACE I/D polymorphism on responsiveness to exercise training. Of the eight studies, four studies (Colakoglu et al. 2005, Pescatello et al. 2006, Giaccaglia et al. 2008, Folland et al. 2000) had reported that D alleles of ACE I/D polymorphism demonstrated greater strength gains compared to I alleles (percentage range of strength gains in all four studies was 14.3% to 38 %; Cohen d = 0.07 to 2.00). On the other hand, three studies (Williams et al. 2005, Thomis et al. 2004, Charbonneau et al. 2008) had reported no significant association between the D alleles and response to strength training. Only one study (Lima et al. 2011) had shown that individuals with II genotypes demonstrated significant training x genotype interaction and greater strength gain compared to DD and ID genotypes (percentage change 5.3, 1, 2.3% for II, ID and DD, respectively) in response to of knee extensor strength conditioning.

Table 6.1 summarises the studies of ACE I/D genotypes and their influence in response to training that were included in the systematic review of chapter three. Presently the gene-environment interaction between candidate genotypes of gene polymorphisms and responsiveness (rate of strength gain) to physical conditioning is still largely understudied (Beunen et al. 2010). In addition, there are no previous studies that have considered the genetic influence on responsiveness to strength training programme in rehabilitative setting. Therefore any study investigating the effects of gene-environment interaction in the responsiveness of patients to physical conditioning protocols could be an important study that might interpret the outcomes contributing towards successful ACLR rehabilitation.

From a clinical perspective, a better understanding of the role of candidate genotypes of gene polymorphism in the regulation of muscular strength and the adaptation would be useful for medical staff and scientists working in rehabilitative and sports performance settings. If it is possible to successfully identify 'high' and 'low' exercise responders before prescribing an exercise program according to their ACE genotype, then it would seem realistic to tailor exercise or training programs according to the individuals' response-capability in order to optimise the outcomes of rehabilitation. This will in turn be advantageous in facilitating the achievement of optimal level of performance required following ACLR surgery (Williams et al. 2005).

Table 6.1: A summary of the studies of ACE I/D genotypes and their influence in response to strength training that were included in the systematic review of chapter three

	Study	Type of study	Subjects, activity level	Training intensity and frequency	Training duration	Results
1	Colakoglu et al. (2005)	RCT: 3 groups	99 Caucasian non elite males	SSG & MSG underwent strength-training program (9-11 muscle groups) with 12–15 and 8-12 RM mesocycles.	6 weeks	Subjects with DD had significantly more strength gains in both groups (SSG, MSG)
2	Giaccaglia et al. (2008)	RCT	213 men and women, overweight & obese	Knee extensor strength, walking distance .Self-reported physical disability score.	18 months	DD genotype showed greater gains in knee extensor strength compared to II. Greater improvement in physical disability score in DD genotypes.
3	Lima et al. (2011)	Cross sectional	Old 246 women	Knee extension, hamstrings curl, leg press, hip abduction	24 weeks	In response to RT, II significantly increased FFM and significant training×genotype interaction was found.
4	Pescatello et al. (2006)	Cohort	631 men and women	Elbow flexor/extensor resistance training (nondominant arm),	12 weeks	ID explained 1% of the MVC response to RT in T and 2% of MVC, 2% of 1RM, and 4% of CSA response in UT
5	Folland et al. (2000)	Cross sectional	33 healthy male	Strength training for quadriceps muscles	9 weeks	Significant greater strength gains in subjects with the presence of D allele. Response to isometric training is strongly genotype dependant (II, 9.0 ± 1.7%; ID, 17.6±2.2%; DD, 14.9).
6	Williams et al. (2005)	Cross sectional	81 untrained men, 44 performed	Quadriceps dynamic muscle strength	8 weeks	ACE had no significant association with 9–14% mean increases of muscle strength in response to the training

Table 6.1: A summary of the studies of ACE I/D genotypes and their influence in response to strength training that were included in the systematic review of chapter three

			strength programme			intervention.
7	Charbonneau et al. (2008)	Cohort	86 inactive men, 139 inactive women	Unilateral knee extensor ST (dominant)	10 weeks	No associations observed for 1RM in adaptations to ST in men or women
8	Thomis et al. (2004)	Twin study	57 males: 16 pairs DZ, 25 pairs MZ male	Resistive elbow flexor training	10 weeks	A response to the strength training was not associated with I/D genotype.

Keys:

N/A: Not Applicable, CG: Control Group, RT: Resistance Training, SSG:Single Set Group, MSG:Multiple Set Group, MVC: Maxiaml Voluntary Contraction, DZ: Dizygotic, MZ: Monozygote, FFM:Fat-Free Mass, BW: Body Weight, RT: Resistive Training, PP: Peak Power.

Therefore the aims of this trial are as follows:

6.1.1 Aims of the study

Primary aim

To investigate the influence of ACE I/D genotypes (candidate genotypes responsive to rehabilitative conditioning) on the objective functional (single leg hop) and objective neuromuscular (peak force [PF], RFD, EMD, SMP and ATFD) outcome measures in a clinical population following ACLR surgery and rehabilitation.

Secondary aim

To investigate the relative influence of ACE I/D gene polymorphism (on the objective functional (single leg hop) and objective neuromuscular (peak force [PF], RFD, EMD, SMP and ATFD) outcome measures amongst accelerated and contemporary rehabilitation conditioning following ACLR surgery and rehabilitation.

6.1.2 Research hypothesis

Hypothesis One

Null (*Ho*): there will be no influence of D allele of ACE I/D gene polymorphisms (candidate genotypes responsive to strength conditioning) on the objective functional (single leg hop) and objective neuromuscular (peak force [PF], RFD, EMD, SMP and ATFD) outcome measures of knee in a clinical population following ACLR surgery and rehabilitation.

Alternative: there will be an influence of D allele of ACE I/D gene polymorphisms (candidate genotypes responsive to strength conditioning) on the objective functional (single leg hop) and objective neuromuscular (peak force [PF], RFD, EMD, SMP and ATFD) outcome measures of knee in a clinical population following ACLR surgery and rehabilitation.

Hypothesis Two

Null (*Ho*): there will be no influence of ACE I/D gene polymorphisms on the objective functional (single leg hop) and objective neuromuscular (peak force [PF], RFD, EMD, SMP and ATFD) outcome measures amongst accelerated and contemporary groups following ACLR surgery and rehabilitation.

Alternative: there will be an influence of ACE I/D gene polymorphisms on the objective functional (single leg hop) and objective neuromuscular (peak force [PF], RFD, EMD, SMP and ATFD) outcome measures amongst accelerated and contemporary groups following ACLR surgery and rehabilitation.

6.2 Method

6.2.1 Participants

As mentioned earlier, because the current study had three distinctive studies (chapters four, five and six), participants of the current study were those who participated in the other two trials (see Figure XII for an overview of the three trials). Briefly, patients were treated by five consultant orthopaedic surgeons (PG; SR; AB; SW, RR) of similar experience and practice (> 12 ACL reconstruction surgeries per month) using agreed and matched surgical procedures. Patients who had consented for ACL autologous reconstructive surgery by one of the five surgeons involved in this study and who would be willing to attend RJAH Orthopaedic and District Foundation Trust for rehabilitation were approached. No exclusions were made regarding the autologous graft choice. Patients meeting inclusion criteria from a date specific and randomly-sequenced cohort awaiting surgery or subsequently presenting with injury were offered participation. The patients were contacted approximately one week before the last pre-surgery appointment with their respective surgeons and were given the opportunity to ask further questions about the participation in the study. No exclusions were made on the basis of gender or race. Only patients over 16 years old who were deemed musculoskeletally and mentally mature were invited to take part in the study. Patients suffering with bilateral knee pathologies at the time of consent were excluded as the contra-lateral knee would not suffice as a control. Multiple ligament injuries that would require adaptation to the standard rehabilitative practice were excluded. Patients with systemic conditions such as rheumatoid arthritis, chronic obstructive airways disease or cardiac pathology were excluded on the basis that their physiological responses to training would be compromised and their physical ability to take part in the rehabilitation programmes investigated in this study would prove difficult and clinically inappropriate.

From ethics perspective, the potential risks and benefits of the study were discussed Participants were also provided with Patient Information Sheet (Appendix I) in which full details of the procedures of blood collection, handling of the sample, confidentiality. Patients were made aware that blood sample analysis would involve only the testing of one gene; namely ACE I/D gene polymorphisms. All participants were fully aware that they could withdraw from the study without giving any reason and this would in no way alter the care they received. Patients who were willing to participate in the study were then given Participation Consent Form (Appendix II). This study was approved by the Ethics Committee for Human Testing of the Queen Margaret University, UK, and by the Shropshire area NHS Ethics Committee (REC Reference (11/WM/0417, see Appendix III). After study completion, the blood samples will be disposed (destroyed) in accordance with the Human Tissue Authority Code of Practice.

6.2.2 Blood sample collection

Participants (n=40) lay in a semi-supine position and a venous blood sample (10mL) was obtained from a superficial forearm vein by the staff of phlebotomy department at Robert Jones and Agnes Hunt Hospital (RJAH), Gobowen, Oswestry. U.K. The samples were subsequently collected into a heparin vacutainer (anti-coagulant) tube. All blood samples were initially stored at -20C^0 in a secure place at RJAH and were then transported by a special courier to Napier University, Edinburgh, Scotland (collaborative University) for DNA extraction and the subsequent analysis of biological markers of the candidate gene, namely ACE I/D polymorphism.

6.2.3 DNA extraction

DNA extraction was performed using a genomic purification kit, according to the manufacturer's instructions (Promega®, UK). Briefly, 300 μL of each blood sample was gently mixed with 900 μL cell lysis solution (proprietary formula) and pelleted by centrifugation for 20 s at 12 *x g*; the supernatant was discarded. The remaining pellet was then resuspended in 300 μL nuclei lysis solution (proprietary formula) and 100 μL protein precipitation solution (proprietary formula) was then added to the pellet followed by a 3 min centrifugation at 12,000 *x g*. A new pellet was used following the centrifuge in which Isopropanol solution (300 μL) was added and this was subsequently centrifuged for 1 min. The supernatant was then discarded and 70% (v/v) ethanol (300 μL) was added and the sample was pelleted by centrifugation for 1 min at 12 *x g*. Finally, the ethanol was aspirated and the pellet was left to air dry for 10-15 minutes. The final DNA pellet was then resuspended in 100 μL DNA rehydration solution (proprietary formula) and stored at -20^{o}C until further analysis. Figure 6.1 summarises the procedures of DNA extraction of the current study.

6.2.4 Genotyping of ACE I/D polymorphism

The ACE I/D polymorphism was genotyped by polymerase chain reaction (PCR) and agarose gel electrophoresis. PCR enables sequence-specific amplification of DNA, in this case, a sequence encoding part of the ACE gene. PCRs are carried out in a thermal cycler which enables the reaction to undergo the rapid and accurate temperature changes required for amplification of DNA (Yin et al. 2001).

Analysis of extracted genomic DNA by gel electrophoresis

In order for the PCR to be successful, it was important to verify the integrity of the DNA template. Therefore, prior to starting the PCR, the extracted genomic DNA was analysed by gel electrophoresis. Each genomic DNA sample (2 μL) was mixed with 8 μL dH_2O (to increase sample volume) and 2 μL (10 X) DNA loading buffer. A 1% (w/v) agarose gel was prepared in 1 X TAE buffer (Tris-acetate EDTA; 40mM Tris-base; Sigma-Aldrich®, 20mM glacial acetic acid; Fisher Scientific, UK, 5mM EDTA; pH 8) and 6 μL SafeView® (Ambion, UK). Gels were electrophoresed between 80-100V for 30-60 min. Samples were run alongside a molecular weight markers; Hyperladder IV (Bioline). Genomic DNA was visualised using a UV (ultraviolet) transilluminator (Biorad, UK) at a 80 ms exposure and the images captured and analysed using imaging software. Genomic DNA samples clearly visible on the gel were selected for PCR analysis, any ‘failed’ gDNA extractions were repeated and re-analysed.

Polymerase chain reaction

The extracted gDNA from each participant was then subjected to polymerase chain reaction in order to amplify a region of the ACE gene. Each PCR 50 µL mix contained: 10 µl 5 X buffer (Promega®, UK); 3 µL $MgCl_2$ (1.5 mM final concentration; Promega®); 1 µL deoxynucleotide triphosphate (dNTPs; 1.25mM; Sigma-Aldrich®, UK), 1 µL of each forward and reverse primer (final concentration 300 nM each; see Table 6.2) and GoTaq® flexi DNA polymerase (1.5 U; Promega®) in storage buffer B (20 mM Tris-HCl, pH 8.0; 100 mM KCl; 0.1 mM ethylenediaminetetraacetic acid (EDTA), 1 mM DTT; 50 % (v/v) glycerol; 0.5% (v/v) Tween®20 and 0.5% (v/v) Nonidet®-P40; Promega®), made up to 50 µL with DNase- and RNase-free H_2O. A negative control reaction was always completed concurrently, with the gDNA template omitted, to ensure products were amplified from the gDNA template and not any other contamination source.

The partial ACE gene sequence was amplified using a thermal cycler (Techne®) in a 30-cycle (2.5 h) programme. The standard thermocycling conditions consisted of: an initial denaturation at 95°C for 10 min and then 30 cycles of; denaturation at 94°C for 30 s, annealing at 56°C for 45 s and extension (synthesis) at 72°C for 2 min. There was a final synthesis step at 72°C for 7 minutes. The PCR products were subsequently visualised using agarose gel electrophoresis (as per the method above). The amplified PCR products (D and I alleles) were identified as differently-sized products on the gel. For analysis of the ACE I/D polymorphism, the PCR products had three size possibilities; two fragments of 319 bp and 597 bp for ID genotype (heterozygotes), a single 319 bp fragment for DD genotype (homozygotes) and a single 597 bp fragment for II genotype [homozygotes] (see Figure 6.2).

Table 6.2: The primers (forward and reverse) of ACE gene that were used for DNA analysis using PCR.

Target gene	Forward primer (5’ → 3’)	Reverse primer (5’ → 3’)
ACE	CTGTTGCCTGTGGTAAGTGGG	TGGTCACAGTATGCAGGAGGG

Figure 6.1: The process of DNA extraction.

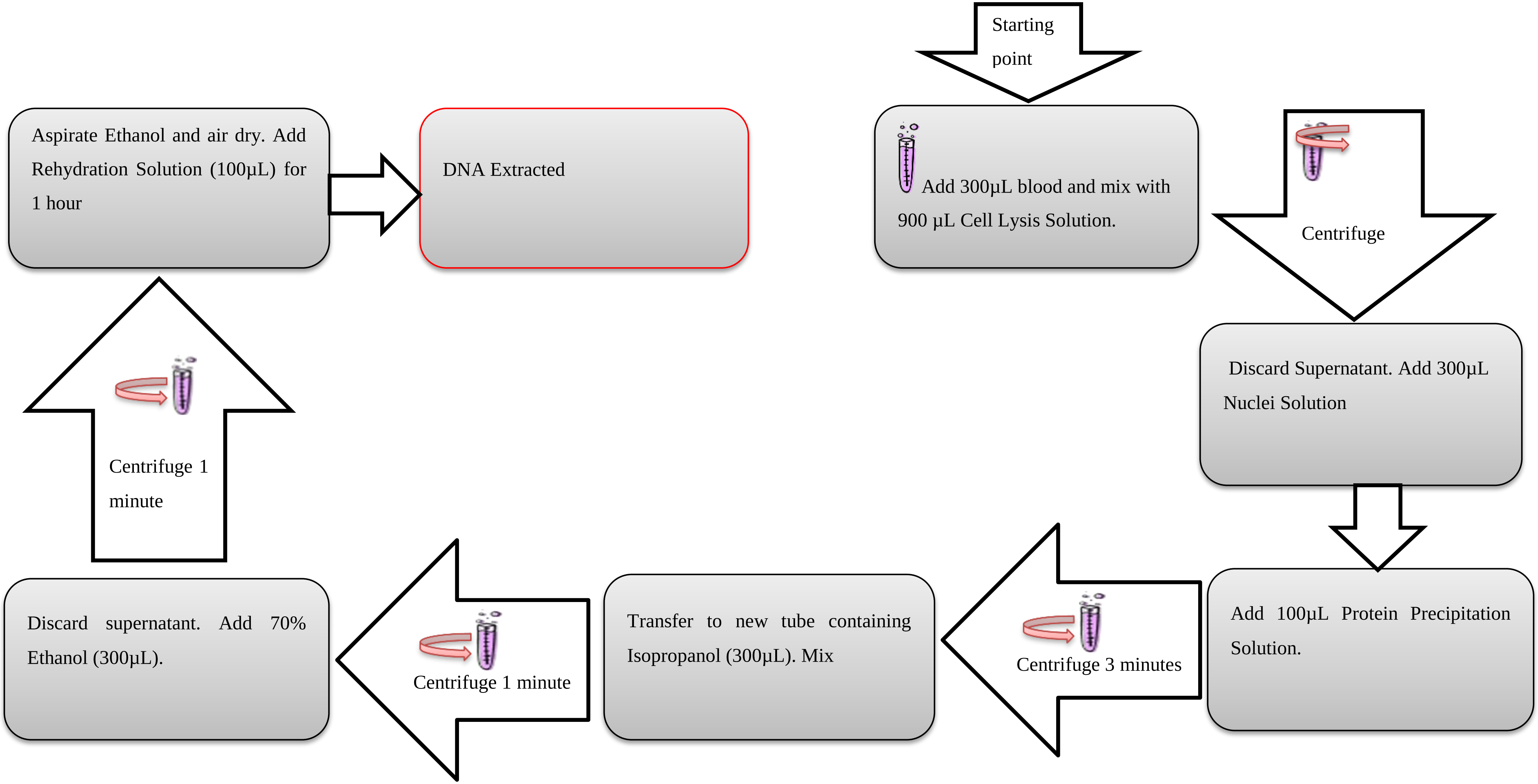
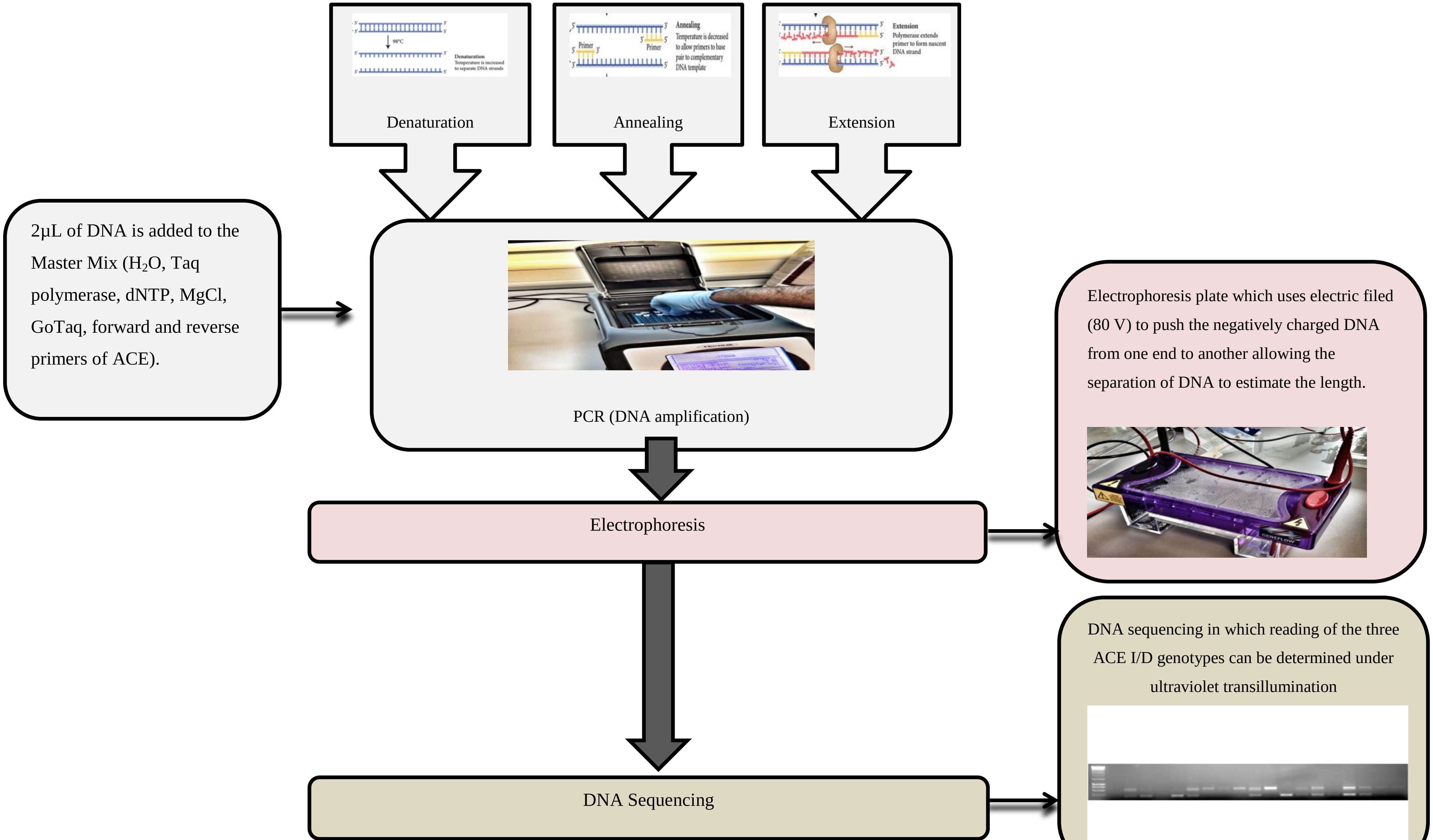


Figure 6.2: The process of PCR and DNA sequencing.



6.2.5 Experimental assessment procedures

Details of the experimental assessment procedures for participants in the current study had been mentioned in chapter four (study one) in which the objective functional (single leg hop), subjective functional outcome measures (Lysholm, K-SES, KOOS and IKDC), objective neuromuscular performances (peak force [PF], electromechanical delay [EMD], rate of force development [RFD] and sensorimotor performance [SMP] of quadriceps and hamstrings musculature and anterior tibio-femoral displacement [ATFD] of knee joint had been used.

6.2.6 Power calculation and statistical analysis

The sample sizes used for this study was consistent with those reported in a previous published study on the relationship between D allele of ACE I/D polymorphism and strength and the response to strength training (Williams et al. 2005). A *priori* alpha level was set at $p<0.05$. The experimental design offered an approximate 0.80 power of avoiding type 2 error when employing at least a detectable difference (a minimum extent of difference between the effects of experimental interventions (accelerated versus contemporary) that might be considered clinically and biologically meaningful in the primary outcomes [single leg hop, IKDC, KOOS, K-SES, Lysholm] (Sport Science 2006). The sample size is also justified based on previous studies. For instance, in the study of Gleeson et al. (2008), the experimental design had offered an approximate 0.80 power of avoiding a Type II error when employing a least detectable difference of 0.2 mm, 16 N, 4ms and 0.3 units during comparisons of ATFD, PF, EMD, and IKDC scores, respectively. Therefore, based on the latter least detectable difference (MCD), an internet-based sample size calculator that has been scientifically verified (Glazier et al. 2010) was used to estimate sample size of this study. It was estimated that 50 participants will be needed [accelerated group (n=25); contemporary group (n=25)] for appropriate experimental design sensitivity and statistical power involving random-allocation to experimental or control groups.

Although previous study (study one, chapter four) of this thesis had shown significant interaction of 3 factors (group; accelerated and contemporary, time; pre-surgery (0), 6, 12 and 24 week post-surgery, leg; injured, uninjured limbs) in patient-reported outcomes of KOOS (pain, quality of life) and in rate of force development (RFD hamstrings), peak force of hamstrings (PF hamstrings) of the accelerated group when controlling for body mass, waiting time and unstructured physical activity, the latter interaction were not clinically meaningful ($r<0.07$). As well as investigating the effects of ACE I/D genotypes on functional, objective and subjective outcome measures of knee performance, the current study will use ACE I/D genotypes as a covariate to evaluate its influence on the latter outcomes. Therefore, repeated measures analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to determine whether the genotypes of ACE I/D had any influence on the outcomes of knee function following ACLR surgery and rehabilitation. The assumptions underpinning the use of repeated measures ANOVA were checked and violations corrected by the Greenhouse-Geisser (GG) adjustment of the critical F-value. Statistical significance was accepted at $p < 0.05$. Although the results of repeated measures ANOVA for absolute scores of measures had been presented in the current study, the absolute scores will however represent the status of a participant at a particular test occasion (e.g. strength status at week 6 post surgery). However, the aim of the current study was to look at the change score (responsiveness) to investigate the influence of accelerated conditioning in the period between pre-surgery (0) to week 12 and between week 12 and week 24 post-surgery. Therefore the focus of the current study would be on the results of change scores (e.g. change scores from pre-surgery (0) to week 12 post-surgery using repeated measures ANCOVA. When grouping the genotypes in SPSS statistical software, the D allele participants (i.e. DD and ID) were combined on the basis of the evidence from the literature surrounding the D-allele and to compare with other studies that had similar experimental design and analyses. Therefore it was hypothesized that the an association would be observed between D allele carriers and greater increases in functional, objective and subjective measures of knee function in response to accelerated training.

6.3 Results

6.3.1 Participant characteristics

Forty adults [men, 34 women, 06; (mean ± sd), age 32.23 ± 12.27 years, 29.60 ± 11.61; height 1.76 ± 0.04, 1.62 ± 0.04 m; body mass; 80.25 ± 9.63, 64.24 ± 8.9 kg] electing to undergo unilateral ACL-reconstructive surgery (central third, bone-patella tendon bone graft, or semitendinosus and gracilis graft) at a U.K. National Health Service Foundation Trust gave their informed consent to participate in the study. No significant differences in anthropometric characteristics (age, weight, BMI and waiting time and unstructured physical activity) between the three ACE genotypes (II, ID and DD) were found.

Table 6.3: The means, standard deviation, F and significant values of age, weight, BMI (anthropometric characteristics) and number of rehabilitation visits amongst the three groups of genotypes (DD, ID and II) of ACE I/D polymorphism.

		N	Mean	Std. Deviation	F ratio	Sig
Height	II	12	174.04	6.79	.23	.79
	ID	19	174.57	7.73		
	DD	9	176.05	4.03		
Visits	II	12	13.66	3.86	.21	.80
	ID	19	14.789	4.90		
	DD	9	14.55	5.19		
Age	II	12	31.75	10.30	.19	.82
	ID	19	30.84	12.48		
	DD	9	33.89	13.56		
Waiting time	II	12	161.25	170.36	.46	.63
	ID	19	146.58	125.94		
	DD	9	204.56	164.41		
BMI	II	12	26.3767	3.939	.84	.43
	ID	19	24.9874	2.561		
	DD	9	25.4033	1.771		

6.3.2 Normality of test

Using Shapiro-Wilk test, there was no difference between the accelerated and contemporary groups in terms of scores of variables of interest at baseline (pre-surgery).

6.3.3 Genotypes distribution and frequency

Genotypes distribution and frequency and of ACE I/D polymorphism were performed using the analysis of chi-square (X^2) test to verify agreement of genotype distribution with Hardy-Weinberg equilibrium. The genotype distribution in the current study was congruent with Hardy-Weinberg equilibrium (X^2= 0.08) and the distribution was 30%, 47.5% and 22.5% for II, ID and DD genotype, respectively (Table 6.4). The frequency of D and I allele was 46 and 54%, respectively.

Table 6.4: The genotype distribution and frequency (%) of ACE I/D polymorphism in the study.

	II	ID	DD
Number of participants	12	19	9
%	30	47.5	22.5

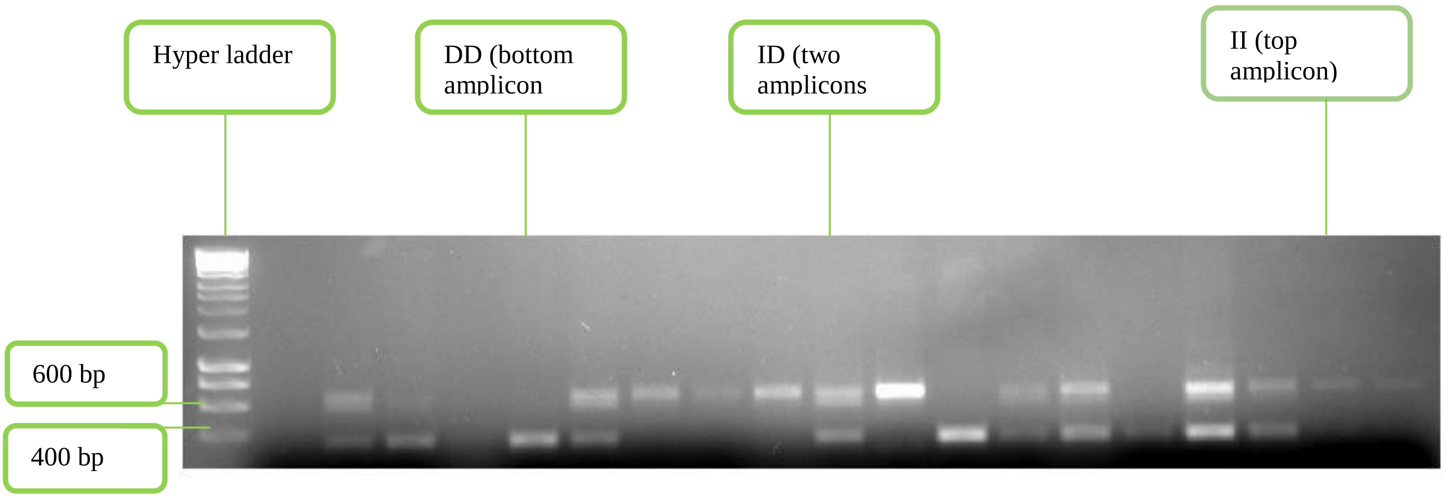


Figure 6.3: An example agarose gel electrophoresis image showing the amplified ACE gDNA from blood samples following PCR and after being exposed to ultraviolet transillumination. All the three possible genotypes of the ACE I/D polymorphism (II, ID and DD) are visible in the image. Hyperladder is used to confirm the size of the amplified DNA molecules (e.g. the small DNA will travel faster through the gel, so the amplicons at 400 bp in the ladder will migrate faster and further than amplicons at 600 bp).

6.3.4 ACE genotype x time x leg interaction

There was no significant interaction neither on 3 way factors ANOVA (ACE genotypes [DD, ID, II] time; pre-surgery (0), 12, 24 weeks post-surgery, leg [injured, uninjured]) with repeated measures on the latter two factors nor 2 way factors with repeated measures on the latter two factor (ACE genotype x time) in change scores (0-12 weeks and 12-24 weeks post-operatively) of the objective functional outcome (single leg hop) [Table 6.5]. The results suggested that the patients in both the D and I allele groups showed similar patterns of single leg hop improvement over time in the injured and uninjured legs during formal ACLR rehabilitations. This result of non-significant interaction was observed across all other outcome measures (peak forces, RFD, EMD of quadriceps and hamstrings, and ATFD).

ACE genotype x time x leg

	ACE	Mean	Std. Deviation	N	P value
Hop injured 0-12 weeks	DD	-14.75	13.06	9	0.15
	ID	-6.63	6.58	19	
	II	-5.17	5.93	12	
Hop uninjured 0-12 weeks	DD	-10.73	8.79	9	
	ID	-10.60	8.73	19	
	II	-8.61	8.79	12	
Hop injured 12-24 weeks	DD	12.90	10.54	9	
	ID	8.25	5.81	19	
	II	7.71	5.70	12	
Hop uninjured 12-24 weeks	DD	11.73	7.06	9	
	ID	12.34	9.09	19	
	II	10.69	8.74	12	

Table 6.5: Table 6.5: Change scores [pre-surgery (0) to12 and 12 to 24 weeks post-surgery] of single leg hop for three way factors (ACE genotypes [DD, ID and II], time [pre-surgery (0), 12, 24 weeks post-surgery, leg [injured, uninjured]).

However, because the D allele carriers (DD and ID alleles) had been shown to be more responsive than the I allele carriers (Folland et al. 2000, Pescatello 2006), the studies of Folland et al. (2000) and Pescatello (2006) had analysed the D allele carriers as one group and the I allele group as another group to evaluate the effect of combined genotypes (DD and ID). For instance, Pescatello et al. (2006) found that 1RM increase was greater for DD and ID allele (7% greater) compared to II allele in untrained arms of a study that examined 631 participants who had upper-arm resistance training (RT) programme in the trained and untrained arms. Based on the literature, the current study had further divided groups into two; the D and I allele groups.

When the D allele (DD and ID) were combined into one group, there was no significant interaction neither on 3 way factors ANOVA (ACE genotypes [DD, ID, II] time; pre-surgery (0), 12, 24 weeks post-surgery, leg [injured, uninjured]) with repeated measures on the latter two factors nor 2 way factors with repeated measures on the latter two factor (ACE genotype x time) in change scores (0-12 weeks and 12-24 weeks post-operatively) of the objective functional outcome (single leg hop) [Table 6.5]. The results suggested that the patients in both the D and I allele groups showed similar patterns of single leg hop improvement over time in the injured and uninjured legs during formal ACLR rehabilitations.

Table 6.6: Change scores [pre-surgery (0) to12 and 12 to 24 weeks post-surgery] of single leg hop for three way factors (ACE genotypes [DD, ID and II], time [pre-surgery (0), 12, 24 weeks post-surgery, leg [injured, uninjured]).

ACE genotype x time x leg

	ACE	Mean	SD	N	P value
Hop injured 0-12	ID,DD	-9.24	9.71	28	
	II	-5.17	5.93	12	
Hop uninjured 0-12	ID,DD	-10.64	8.59	28	
	II	-8.61	8.79	12	0.65
Hop injured 12-24	ID,DD	9.75	7.76	28	
	II	7.71	5.70	12	
Hop uninjured 12-24	ID,DD	12.15	8.37	28	
	II	10.69	8.74	12	

However, there was significant interaction on 3 way factors (ACE genotypes [DD, ID, II] time [pre-surgery (0), 12, 24 weeks post-surgery, leg [injured, uninjured]) in the change scores of peak force of quadriceps (objective neuromuscular outcome measure) [$F_{(1.1,\ 38.2)\ GG}=5.57$, $p=0.02$]. The results suggested that the patients in the D and I allele groups showed different patterns of improvement for peak force of quadriceps over time in the injured and uninjured legs. Group mean scores for peak force of quadriceps suggested that while patients in both the D and I allele groups showed improved performance during the follow-up period, group mean scores associated with the D allele group confirmed superior capability for both legs but that this was more pronounced in the injured leg ($F_{(1.1,\ 38.6)\ GG}= 2.7$; $p=0.03$). A *priori* ‘interaction’ testing of greater change scores in peak force of quadriceps associated with the D versus I allele groups suggested that superior performance for the injured leg at 12-24 weeks post-surgery compared to 0-12 weeks post-surgery ($F_{(1,\ 38)\ GG}=3.2$, $p=0.03$), contributed most to the overall significant interaction for the injured leg of patients in D and I allele groups.

Table 6.7: Change scores [pre-surgery (0) to12 and 12 to 24 weeks post-surgery] of peak force (PF) quadriceps for three ways factors ANOVA (ACE genotypes [DD, ID and II], time [pre-surgery (0), 12, 24 weeks post-surgery, leg [injured, uninjured]).

ACE genotype x time x leg

	ACE	Mean	SD	N	P value
PF quad injured 0-12	ID,DD	-58.03	40.84	28	
	II	-34.91	18.10	12	
PF quad uninjured 0-12	ID,DD	-37.88	21.06	28	
	II	-37.45	13.53	12	
PF quad injured 12-24	ID,DD	98.48	38.43	28	0.02
	II	64.97	34.14	12	
PF quad uninjured 12-24	ID,DD	30.05	26.84	28	
	II	37.17	25.94	12	

No significant interaction was found neither on 3 way factors ANOVA (ACE genotypes [DD, ID, II] time [pre-surgery (0), 12, 24 weeks post-surgery, leg [injured, uninjured]) nor on 2 way factors (ACE genotype x time) in the change scores of objective neuromuscular measures of RFD ($F_{(1,38)GG}$=1.38; ns), ($F_{(1,38)GG}$=0.84; ns), EMD ($F_{(1,38)GG}$=1.12; ns), ($F_{(1,38)GG}$=0.38; ns) SMP ($F_{(1,38)GG}$=1.67; ns), ($F_{(1,38)GG}$=1.11; ns) and ATFD($F_{(1,38)GG}$=0.77; ns), ($F_{(1,38)GG}$=0.53; ns) for quadriceps and hamstrings, respectively. This pattern of non-significant interaction was also observed in the absolute scores of the latter measures. Table 6.7 shows the percentage change scores [pre-surgery (0) to 12 and 12 to 24 weeks post-surgery] of the functional and objective neuromuscular measures of knee.

	Genotype	0-12 weeks % change	12-24 weeks % change
Hop injured 0-12	DD,ID	-26.3	
	II	-19.6	
Hop injured 12-24	DD,ID		9.7
	II		7.7
PFq injured 0-12	DD,ID	-58.0	
	II	-34.9	
PFq injured 12-24	DD,ID		98.4
	II		64.9
PFh injured 0-12	DD,ID	-20	
	II	-27.3	
PFh injured 12-24	DD,ID		17.8
	II		21.7
RFDq injured 0-12	DD,ID	103.7	
	II	128.7	
RFDq injured 12-24	DD,ID		124.2
	II		47.9
RFDh injured 0-12	DD,ID	-378.0	
	II	-217.5	
RFDh injured 12-24	DD,ID		170.5
	II		212.1
EMDq injured 0-12	DD,ID	4.4	
	II	3.9	
EMDq injured 12-24	DD,ID		-4.4
	II		-4.2
EMDh injured 0-12	DD,ID	7.9	
	II	7.8	
EMDh injured 12-24	DD,ID		-3.9
	II		-4.7
ATFD injured 0-12	DD,ID	-4	
	II	-2.8	
ATFD injured 12-24	DD,ID		0.26
	II		0.023
SMPq injured 0-12	DD,ID	52.3	
	II	44.7	
SMPh injured 12-24	DD,ID		43.2
	II		37.4

Keys: PFq: peak force quadriceps, PFh: peak force hamstrings, RFDq: rate of force development quadriceps, RFDh: rate of force development hamstrings, EMDq: electromechanical delay quadriceps, EMDh: electromechanical delay hamstrings, ATFD: anterior tibio-femoral displacement, SMPq: sensorimotor quadriceps, SMPh: sensorimotor hamstrings.

Table 6.8: The percentage change scores [pre-surgery (0) to 12 and 12 to 24 weeks post-surgery) for the injured legs in the objective functional (hop) and objective neuromuscular outcome measures (PF, EMD, RFD, SMP, ATFD) of knee.

6.3.5 Influence on the knee outcomes when controlling for ACE I/D polymorphism during ACLR rehabilitation

While repeated measures ANOVA had shown significant interaction in peak force of quadriceps, no significant interaction was found neither on 3 way factors ANCOVA (group [accelerated, contemporary], time [pre-surgery (0), 12, 24 weeks post-surgery, leg [injured, uninjured]) with repeated measures of the latter two factors in the objective neuromuscular outcome measure of peak force for quadriceps musculature ($F_{(1,\ 37)\ GG}$= 5.4; ns) when controlling for ACE I/D polymorphism. This pattern of non-significant interaction was also observed on 2 way factors (group x time with repeated measure on the latter factor).

Similar pattern of non-significant interaction was found on 3 way factors ANCOVA (group [accelerated, contemporary], time [pre-surgery (0), 12, 24 weeks post-surgery, leg [injured, uninjured]) and on 2 way factors (group x time) in the objective neuromuscular outcome measures of RFD ($F_{(1,37)GG}$=0.97; ns), ($F_{(1,37)GG}$=0.88; ns), EMD ($F_{(1,37)GG}$=0.21; ns), ($F_{(1,37)GG}$=0.98; ns) SMP ($F_{(1,37)GG}$=1.33; ns), ($F_{(1,37)GG}$=2.11; ns) and ATFD($F_{(1,37)GG}$=1.76; ns), ($F_{(1,37)GG}$=0.73; ns) for quadriceps and hamstrings, respectively. This pattern of non-significant interaction was also observed in the absolute scores of the latter measures. Table 6.8 shows the percentage change scores [pre-surgery (0) to 12 and 12 to 24 weeks post-surgery) of the functional and objective neuromuscular measures of knee.

6.4 Discussion

For simplicity, the discussion will be divided into four parts; 1) Are patients with the D allele more responsive to rehabilitative training than those with the I allele in a clinical population following ACLR surgery and rehabilitation? 2) What is the relative influence of

ACE I/D gene polymorphism on the responsiveness of outcomes amongst patients who underwent accelerated and contemporary rehabilitation conditioning following ACLR surgery? 3) Clinical implication and 4) Study limitation and conclusion.

6.4.1 Are patients with the D allele more responsive to rehabilitative training than those with the I allele in a clinical population following ACLR surgery and rehabilitation?

As previous studies had shown that individuals with the D allele had greater strength gains than II allele carriers (Colakoglu et al. 2005, Giaccaglia et al. 2008, Pescatello et al. 2006, Folland et al. 2000), the results of the current study had shown significant interaction using 3 way factors (ACE genotypes [DD, ID, II] time [pre-surgery (0), 12 and 24 weeks post-surgery], leg [injured, uninjured]) in the change scores of peak force for quadriceps with superiority of strength gains between the period 12 to 24 weeks post-surgery favouring DD and ID (D allele group) over the II genotype group. This implies that the pattern of improvement in the peak force of quadriceps for the injured and uninjured legs was different overtime in the D and I allele groups with superiority observed in the D allele group and that improvement being more prominent in the late phase (12 to 24 weeks post-surgery) of rehabilitation. The relative effect sizes (Cohen's *d*) for the absolute peak force of quadriceps strength gains over congruent periods of 12 to 24 weeks post-surgery for the D allele group over the I allele carriers was 0.67. The most important feature of this interaction was the extent of percentage change scores (12-24 weeks post-surgery) in the peak force of quadriceps for the DD and ID genotype group (98.4% versus 64.9% for the II genotype group). Although this might explain 15% of the total variance of peak force for quadriceps that is attributable to ACE D allele, the latter finding might possibly justify the rationale for changing the delivery of rehabilitative care as patients with the D allele demonstrated better response to rehabilitative training. Although the majority (4 out 5) of the objective functional (single leg hop) and objective neuromuscular outcome measures (EMD, RFD, SMP) had shown no statistically significant interaction in response to rehabilitative training, the specific types of rehabilitation involving accelerated conditioning within the current study were designed to primarily improve strength status rather than the patient's functional status (single leg hop), reaction time (EMD), force generation (RFD) and muscle re-education following ACL injury disruption (SMP). The finding of statistical interaction of peak force for quadriceps was therefore expected especially due to the fact that the correlation study (chapter five, study two) had found either poor or no correlation linking muscular strength to EMD, RFD or SMP. In addition, at 12 weeks post-surgery, the percentage change scores in the current study were higher than those reported in the study of Folland et al. (2000) [II;9%, ID; 17.6%, DD; 14.9%] who introduced quadriceps strength training for 9 weeks in 33 healthy males participants. The possible explanation for this could be the fact that the clinical population in the current study had experienced deconditioning following ACLR surgery, and thus demonstrated quicker recovery rate in the peak forces in comparison to the healthy population in the study of Folland et al. (2000). However, Giaccaglia et al. (2008) found that participants homozygous for the D allele demonstrated higher percentage change scores (66% versus 6 and -2% for the ID and II genotypes, respectively) than those reported in the current study following an 18 month exercise training intervention. Therefore, intra-genotypic responses to conditioning were heterogeneous for strength gains over different periods of training and that duration, intensity and frequency of strength conditioning are potential factors that contribute expectedly to the differential responses of genotypes in regulating gains in strength.

In contrast, there was no significant interaction using 3 way factors (ACE genotype by leg by time) and 2 way factors (ACE by time) in the change scores of single leg hop, RFD, EMD and SMP between the period from pre-surgery (0) to 12 weeks post-surgery and 12 to 24 weeks post-surgery. This pattern of non-significant interaction was also observed in the absolute scores of the latter outcome measures. It might be speculated that because an interaction in the peak force of quadriceps had been observed in the current study, this would not necessarily be associated with a significant interaction observed in other objective neuromuscular outcome measures such as EMD, RFD and SMP as these outcome measures are not directly linked as shown in the correlation chapter (chapter five).

6.4.2 What is the relative influence of ACE I/D gene polymorphism on the responsiveness of outcomes amongst patients who underwent accelerated and contemporary rehabilitation conditioning following ACLR surgery?

In addition to the investigation of whether or not the D allele carriers had greater objective functional and objective neuromuscular gains (responsiveness) in the outcome measures of knee performance following ACLR surgery and rehabilitation, the secondary aim of the current study was to investigate the relative influence of ACE I/D genotypes on the responsiveness of outcomes amongst patients who underwent accelerated and contemporary rehabilitation conditioning following ACLR surgery. As study one (chapter four) of this thesis demonstrated, factors including waiting time, body mas and unstructured physical activity had an influence on the outcome measures of knee function. While using ANOVA

(ACE genotype by leg by time factors) in section 6.4.3 had shown significant interaction for peak force of quadriceps, no significant interaction was found when using the ACE I/D polymorphism as a covariate (ANCOVA; group [accelerated, contemporary] by time [pre-surgery (0), 12 and 24 weeks post-surgery by leg [injured, uninjured]) in the objective neuromuscular measures of peak force of quadriceps musculature. While the study in section 6.4.3 essentially pooled the 'groups' (groups divided on the basis of ACE genotypes), the results in this section suggested that there were similar patterns of improvement in both the accelerated and contemporary groups for the peak force of quadriceps in the injured and uninjured legs over time. A similar pattern of non-significant interaction was also noted using two way factors (group by time), suggesting the two groups had not been differentially influenced by the injured and uninjured legs.

In general, when controlling for ACE I/D polymorphism, no significant interaction was found using 3 way factors ANOVA (group [accelerated, contemporary], time [pre-surgery (0), 12 and 24 weeks post-surgery, leg [injured, uninjured]) in the functional (single leg hop) and the objective neuromuscular (PF, EMD, RFD, SMP and ATFD) outcome measures following ACLR rehabilitation. In comparison to the previous study (study one, chapter four) that demonstrated a statistically significant interaction (group by leg by time) in the outcome measures of peak force and RFD for hamstrings when statistically controlling for anthropometric factors (waiting time, body mas and unstructured physical activity), the current study had not shown significant 3 way interaction on the objective functional and objective neuromuscular measure of knee following ACLR rehabilitation. This suggests that ACE I/D genotypes had no influence on determining the objective functional and neuromuscular outcomes of knee following ACLR rehabilitation.

6.4.3 Implications for clinical practice

It is hoped that this current trial highlighted the long-standing challenges to wholly understanding the mechanisms of interaction with genetic variation (i.e genotypic variation in the context of this study) and the regulation of responsiveness to rehabilitative training. Health care providers including physiotherapists could potentially benefit from the assessment of genotypic variation and performance capabilities in determining individual responsiveness to exercise conditioning thus facilitating the advocacy of better, more effective, efficient and individualised rehabilitative programmes.

While the current study had shown statistical significant interaction (ACE genotype by leg by time) favouring the D allele carrier over the I allele carrier group in the strength gains (change scores) of peak force for quadriceps at 12-24 weeks post-surgery, this interaction was not observed when controlling for ACE I/D polymorphism that examined its influence on the outcomes in both the accelerated and contemporary groups. However, it is plausible that the features of ACLR rehabilitation conditioning in both groups (accelerated and contemporary) were essentially accelerated-related due to the fact that the Oswestry rehabilitation programme (contemporary) has some components of acceleration as previously mentioned in chapter four. Therefore this might explain the interaction observed in the peak forces for quadriceps and not in the outcome measures of EMD, RFD, SMP and single leg hop. It could be speculated that designing strength-related exercises (conditioning) is deemed an easier intervention to offer during ACLR rehabilitation compared to those focusing on the improvement of functional status (single leg hop), reaction time (EMD), force generation (RFD) and muscle re-education following ACL injury disruption (SMP). However the finding of the current study offers the possibility of prescribing accelerated rehabilitative programmes to those patients who might genetically be able to respond most effectively to rehabilitation programmes that involve accelerated conditioning. Such an approach will enhance the individualised care of patient as well as reduce the economic burden on health systems.

6.4.4 Limitation and future direction

Given that the effect size of candidate genotypes within gene polymorphisms on exercise-related traits is generally thought to be small, the sample size required to achieve robust statistical significance to reliably achieve or capture such effect sizes will be large (Rankinen et al. 2006). The studies published to date on exercise genetics and the adaptation to exercise programme are underpowered indicating the importance of recruiting much larger sample sizes. Similarly the current study had not achieved the minimal estimated sample size (n=50) to detect phenotype differences between the genotype groups (Charbonneau et al. 2008). Therefore because of the small sample size in this study, the proportion of variance attributable to ACE genotypes would therefore be deemed very small and the analysis of this study should be considered exploratory. In addition, with the fact that the physical activity phenotype is a complex trait, Eynon et al. (2011) claimed that the effect of a single gene variant in this context is small. This view was also supported by Hand et al. (2007) who found a significant combined IGF1 CA repeat main effect and IGF1 CA repeat x PPP3R1 insertion-deletion (I/D) gene by gene interaction effect, on the changes in muscle phenotypic response to strength conditioning following a 10 week unilateral knee extension strength programme. Future studies might focus on examining more than one gene polymorphism in order to understand the true response of individuals to rehabilitative training.

6.5 Conclusion

There are several gene polymorphisms that contribute to the differential response to strength training and ACE I/D polymorphism is one of them. The finding of the current study has demonstrated that the ACE D allele group (DD and ID genotypes) were having significant interaction with rates of adaptation for peak force of quadriceps in the accelerated rehabilitation group. Although the current study was exploratory, it does however offer some evidence to suggest that rehabilitative care for a clinical population with ACLR surgery might be changed on the basis of individual’s genotype (the D allele carriers of ACE I/D polymorphism) which might be an influential and contributing factor to optimise the objective functional and objective neuromuscular outcomes of knee performance following ACLR surgery. Given that physical performance is complex phenotypes, future studies investigating the effects of more than one gene polymorphism could answer the questions related to the clinical implication of gene polymorphism and its genotypes in terms of responsiveness to rehabilitative training.

7 Chapter Seven: General Discussion of the Thesis

7.1 Introduction

This thesis set out to make a novel approach in relation to elucidating the effects of accelerated conditioning rehabilitation on the objective functional (single leg hop), subjective functional (IKDC, KOOS, K-SES and Lysholm) and objective neuromuscular outcome measures (peak force, EMD, RFD, SMP and ATFD) of knee performance. It also set out to understand the relationship (correlation) amongst the latter outcomes as well as the influence of ACE I/D gene polymorphism and its genotypes on the knee outcomes in clinical population who underwent ACLR surgery and rehabilitation. The purpose of this chapter is to consider and synthesise in greater depth the findings from the three empirical studies (chapters four, five and six) of this thesis with each one addressing a specific question. The chapter will also reflect and evaluate the findings in the context of the existing literature. In addition the chapter will discuss the limitations of the studies and the possible implications that might be considered in the future research. Lastly, recommendations for future research will be made with regards to implementing accelerated rehabilitation, the relationship amongst the knee outcome measures and the relative influence of ACE I/D polymorphism. For simplicity, this general discussion will be divided into five main sub-sections; A) Did the accelerated conditioning rehabilitation have any effect on the outcomes of knee in ACLR clinical population? B) Were there any correlation amongst knee function (objective and patient-reported outcomes) and objective neuromuscular outcome measures in ACLR clinical population, C) Did ACE I/D gene polymorphism and its genotypes have any influence on the knee outcomes in ACLR clinical population, D) Limitation of the studies and e) Future recommendations.

A) Did the accelerated conditioning rehabilitation have any effect on the outcomes of knee performance in ACLR clinical population?

As outlined in the systematic review of the thesis (chapter two), five out of ten systematic reviews investigating the effectiveness of accelerated rehabilitation demonstrated moderate effect sizes (Cohen's $d = 0.33$) in terms of improved knee laxity, neuromuscular performance, ROM restoration and patient self-reported outcome measures. In addition, only three out of ten studies in the systematic review had offered FIT (frequency, intensity and time) in some accelerated-related exercises with the means of number of sessions/week, sets, weight, time and period of intervention were 3, 3, 70% repetition maximum (RM), 30 minutes and 7.25 weeks, respectively. Therefore, there is little evidence to contextualise the components of quantified accelerated rehabilitation and the influence of quantified dose-response associated with accelerated conditioning during the ACLR rehabilitation period.

Although all studies included in the systematic review (chapter two) have deployed accelerated rehabilitation, it was noticeable that some author's definition to the term 'accelerated rehabilitation' was not consistent to the principles of accelerated protocol that was introduced by Shelbourne and Nitz in 1990. For instance amongst the rejected studies in the review, Vadalà et al. (2007) had an 'accelerated rehabilitation group' in which participants were instructed to be brace free compared to the control group that had a 'brace on' in the early phase (2 weeks post-surgery) of ACLR rehabilitation. Therefore, the term "accelerated" rehabilitation seems to be inappropriate or unnecessary to use especially with the emergence of more evidence based practice and the continuous shift in the rehabilitation following ACLR surgery. The lack of support for the term 'accelerated rehabilitation' was evident in the review of De Carlo and McDivitt (2006) who thought that the latter term may cause confusion amongst therapists given the shift in rehabilitation trends over the past decade. Based on the review of data, therapists should not be very concerned with the 'term' given to the rehabilitation of ACLR surgery but rather to look at the contents and the time frame at which the exercises were prescribed during the rehabilitation. With more evidence that quadriceps femoris muscle function is an essential part of ACLR rehabilitation, clinicians and therapists may need to combine both neuromuscular and strength training exercises to provide optimal training stimuli at an early stage of ACLR rehabilitation programme. Therefore, based on the systematic review and the research undertaken in the thesis, from the author's perspective, the term "accelerated" could be changed to "**enhanced**" rehabilitation that can be defined as a 'programme that offers early introduction of strength- and neuromuscular- related exercises thought to cause safe strain to ACL compared to the traditional rehabilitation following ACLR surgery'. The 'enhanced rehabilitation' programme therefore aims to achieve the rehabilitation milestones earlier than the traditional rehabilitation programme in terms of regaining full knee extension, weight bearing and normal neuromuscular strength and function of the knee.

Study one:

Changes in objective and subjective functional outcomes

Hop tests have been commonly used in the literature to assess the knee function as well athlete's readiness to resume sporting activities (Yimaz and Baltaci 2006, Logerstedt et al. 2012). It has also been associated with the prediction of subjective patient-reported knee function in patients with ACLR surgery (Logerstedt et al. 2012). Of the objective and subjective functional outcome measures, only KOOS (pain and quality of life sub-sections) had demonstrated significant interaction (group by leg by time ANOVA) with superior results in the accelerated group at pre-surgery to 12 weeks post-surgery. No other significant interaction either on 3 way or 2 way factors for the other functional outcome measures. It might be plausible that KOOS holds the advantage over the other patient-reported outcome measure (IKDC, K-SES and Lysholm) as KOOS separates the scores of each sub-section thus allowing better interpretation and correlation between the items of each subsection (Roos and Lohmander 2003).

Despite the fact there was increased exercise stress associated with accelerated conditioning group, it was interesting to observe that both groups had managed to achieve more than 85% LSI for single leg hop performance at 12 weeks post-surgery (LSI ranged between 88% to 124%). Although the latter percentage changes are consistent with those reported in the study of Reid et al. (2007) and Kvist (2004) at 24 weeks post-surgery (LSI of 82 %, 92 %, respectively), the LSI percentage change in the current study had not exceeded an MCID [the differences within the accelerated and contemporary groups] of 5% (Reid et al. 2007), neither between pre-surgery to 12 weeks post-surgery (110.8, 113.5 %, respectively), nor between pre-surgery to 24 weeks post-surgery (112.7 %, 113.8 %, respectively). However, while the LSI serve to use uninjured side as control, the non-significant findings in the current study might be attributed to the deconditioning of the contra-lateral leg [a decrease in neural drive to both injured and uninjured legs due to a lowered afferent neurologic activity (Wojtys and Huston 2000)]. Indeed the study of Wojtys and Huston (2000) had highlighted this issue and suggested that having a control group with no history of knee injury would serve better than the uninjured side of a patient. Overall, the non-significant interaction in the other functional outcome measures imply that there was no adverse effects on the objective functional (single leg hop) and subjective functional outcome measures (IKDC, K-SES and Lysholm) in the accelerated group following ACLR rehabilitation. It is plausible that improved outcomes of single hop performance could have been observed should the accelerated conditioning continued beyond 12 weeks post-surgery. However the latter conditioning was withdrawn by week 12 post-surgery in order to minimise the unequal iso-volumetric exercise dose between the accelerated and contemporary group.

With regards to MCID of subjective patient-reported outcomes, IKDC and KOOS scores had exceeded the MCID scores (IKDC; 24.4 and 22.2 points, KOOS pain; 5.8 and 7.5 points, KOOS quality of life; 6.5 and 5.8 points for accelerated and contemporary, respectively, at 24 weeks post-surgery) with higher scores mainly in the accelerated group, indicating that it was possible to separate between patients who perceive themselves "improved" from those who didn't in both groups. These findings were consistent to the findings of Collins et al. (2011) and Roos and Lohmander (2003) who reported 6-12 and 10 unit points, respectively, of improvement across all the five sub-sections as the cut-off points for KOOS sub-sections at 6 months following ACLR surgery.

Changes in objective neuromuscular outcomes

As the current study had randomly allocated patients without stratifying them on the basis of anthropometric and orthopaedic-related factors, their features were not expected to directly influence the results of the current study. However, significant interactions using three way factors (group by leg by time) for change scores of single-leg hop had been observed when statistically adjusting for body mass, unstructured physical activity and waiting time with superior change scores in the accelerated group (injured leg) at pre-surgery to 12 weeks post-surgery. Similar patterns of significant 3 way interaction had been observed in the change scores of peak force and RFD for hamstrings with superior change scores in the accelerated group (injured leg) at pre-surgery to 12 weeks post-surgery. This suggests that the orthopaedic-related factors were influential over time in determining the outcomes of ACLR rehabilitation. In consistency with these results, the studies of Beynnon et al. (2011) and Risberg and

Holm (2009) [mentioned in the systematic review, chapter two] had demonstrated significant improvement in knee flexors in the accelerated conditioning group. However it might be argued that the latter two studies had introduced early quadriceps-based exercises (OKC) to patients who had BPTB graft and not hamstrings graft as in the case of study one of this thesis. Nevertheless, the significant improvement in hamstrings strength observed in the current study was incongruent to the study of Tagesson et al. (2008) who found no significant difference in the hamstrings strength between OKC group (early 11 weeks intervention programme) and no OKC group. The patients of the latter study however were a mixture of both BPTB and hamstring grafts. It was unexpected that the current study would continue to show the pattern of hamstrings improvement in the change scores of rate of force development (with superior scores in the accelerated group) as the majority of participants in the current study (92%) had hamstrings graft, meaning that compromise to hamstrings strength was expected during the rehabilitation. However the latter result suggests that the hamstrings musculature had not been adversely affected in the accelerated group and that quicker rate of recovery had been observed in the latter group during the acute phase of rehabilitation.

On the other hand, although previous studies underlined the significant role of quadriceps in maintaining the dynamic knee joint stability and restoring the knee ROM (Heijne and Werner 2007, Shaw et al. 2005), the results of study one had not shared this view as no significant difference was noted between the accelerated and contemporary groups. However, the lack of statistical interaction (on 3 and 2 way factors) in the change scores of peak force for quadriceps suggests no detrimental effect had taken place in the latter musculature. EMD plays an important role in maintaining neuromuscular reaction time which is required during forces of unrestricted development and sufficient magnitude capable of damaging ligamentous tissue in synovial joints (Gleeson et al. 2005, Wojtys and Huston 2000). The fact that both groups in the current study demonstrated no significant interaction in the change scores of EMD suggesting that both groups had experienced reduced neurologic drive which could be attributed to the long waiting time to surgery (Wojtys and Huston 2000).

While no significant difference had been observed between the two groups with respect to increased knee laxity (ATFD), Kvist (2004) argued that measuring laxity in resting position (static) had shown no correlation with other outcomes. The latter author suggested therefore that laxity assessment could present more meaningful results if tested during movement especially with the fact that patients are able to control knee joint during such movement. Importantly this study had reported lower ATFD scores in the accelerated group compared to the contemporary at all test occasions (7.1 ± 1.3 vs 7.5 ± 1.2, 3.2 ± 1.4 vs 3 ± 1.2, 3.9 ± 1.1 vs 3.3 ± 0.9 in week 6, 12 and 24 post-surgery, respectively). This is consistent with the results of Shelbourne and Gray (1997) who demonstrated that about 98% of patients had a laxity of less than 5 mm in a 2 to 9 year follow-up after ACLR surgery. In summary, it seems therefore that controlling for factors of waiting time, body mass and the unstructured physical activity at week 12 post-surgery were the only influential factors that played role in determining the significant changes of patient's functional performance (single leg hop) during ACLR rehabilitation. Table 7.1 shows a summary of the key findings of study one (chapter four).

Key findings of study one	ANOVA (group by leg by time)	ANCOVA (body mass/unstructured physical activity/waiting time by leg by time)	Factors influencing outcomes	Outcomes exceeding MCID
Did the accelerated conditioning rehabilitation have any effect on the outcomes of knee performance in ACLR clinical population?	Greater improvement in KOOS (pain and quality of life) change scores in accelerated group at pre-surgery to 12 weeks post-surgery	Greater improvement in single leg hop, peak force and RFD of hamstrings change scores in accelerated group (injured leg) at pre- to 12 weeks post-surgery	Body mass, waiting time and unstructured physical activity	IKDC and KOOS in accelerated and contemporary groups at 24 weeks post-surgery

Table 7.1: Key findings of study one (chapter four).

Influence of structured physical activity (increased dosage of accelerated conditioning).

One of the novel approaches of this study was to quantify the increased frequency and intensity of exercise stress associated with both the accelerated and contemporary groups. The number of rehabilitation sessions attended in the first 12 weeks after ACLR surgery in the current study (study one) was 12 compared to 36 sessions in the study of Beynnon et al. 2011. Although the 12 sessions attended in the first 12 weeks (early accelerated conditioning phase) corresponded to 83% of the total 14.4 sessions in the accelerated group in this study, it is plausible that 12 sessions might not have been sufficient enough to make an impact on patient's improvement in knee outcome measures following ACLR surgery.

In summary, the fact that there was no frequent significant interaction in the change score of outcomes between the two groups in the late phase (12 to 24 weeks post-surgery) after withdrawing the accelerated conditioning suggests that accelerated conditioning had no detrimental effect on the outcomes of knee in the intervention phase (pre-surgery to 12 weeks post-surgery). The statistically significant interaction observed when controlling for waiting time, body mass and unstructured physical activity might be clinically meaningful for patients given the fact the scores of KOOS and IKDC had exceeded the MCID scores.

Moreover, the accelerated conditioning intervention can be considered successful in the current study as no adverse effects have been associated with patient's progress during ACLR rehabilitation. More importantly, the outcomes of accelerated programme had been matched with those of the current contemporary practice. Indeed, the verification of increased frequency and intensity of exercise stress (dosage) associated with 'structured' rehabilitation has been one of the advantages of the current study. The latter had allowed greater precision with regards to recoding the dosage associated with both accelerated and contemporary rehabilitation programmes. In addition, the unstructured' physical activity (home and leisure-based activity) of exercise stress had also been quantified in an attempt to precisely measure the overall dosage of exercise-related stress during ACLR rehabilitation. A gain of 12% in the functional and neuromuscular performance outcomes had been reported as clinically significant in the literature (Bailey et al. 2003), and if such gain could be achieved before the 'withdrawal' of the experimental stimulus, then the latter stimulus would be considered clinically substantive. Therefore the continuation of accelerated conditioning beyond 12 weeks post-surgery might be justifiable as it will maintain or enhance clinical efficacy during ACLR rehabilitation.

B) Were there any correlations amongst knee objective functional, subjective functional and objective neuromuscular outcome measures in ACLR clinical population?

A gap between participant's perception and the quantified objective knee measures might result in poor rehabilitation planning and if one measure is selected over the other then an unjustifiable bias might be introduced in the process of making progression during ACLR rehabilitation (Ardern et al. 2011). It might conversely be that if patients don't feel functionally capable, due to fear probably (Ardern et al. 2011, Heijne et al. 2007), sub-optimal efforts in ACLR rehabilitation might be reflected in the objective measures as a result. Therefore, having a relationship or a matching between the subjective and objective knee measures would provide the ideal platform in which an appropriate decision for rehabilitation's progress could be established.

Study two:

Relationship between objective and subjective measures of knee performance

A priori expectation in the current study was to observe positive correlations between the absolute scores of objective and subjective outcome measures over time. The finding had shown small correlation between the absolute scores of objective functional measure (single leg hop) and subjective functional measures (KOOS, K-SES, Lysholm and IKDC) [$r=0.38$ with K-SES (PA), 0.35 with KOOS (P), 0.32 with Lysholm, and 0.12 with IKDC, $p>0.05$] at 12 week post-surgery. While these findings were congruent to the poor correlations between IKDC and single leg hop measures demonstrated in the studies of Sernert et al. (1999) and Hurd et al. (2008), the findings of study two suggests that no meaningful clinical relationship could be established between the two measures (objective and subjective functional outcome measures). The latter findings might also suggest that both the single leg hop and subjective patient-reported outcomes are fundamentally independent measures that inform the description of patients' functionality. It was interesting to note that although IKDC have been used extensively in the literature to predict knee functional performance following ACLR, no correlation was found between the latter inventory and any of the objective neuromuscular measures. The implication of the latter finding was that because both measures (subjective and objective measures) are expected to assess the same capability (i.e. knee functional performance), disassociation between them might lead to compromised rehabilitation that might undermine the importance of either the objective capability of patient or the self-perceived capability of the patient in terms of knee function. The latter mismatch might therefore have an adverse effect when designing an appropriate rehabilitation programme that should be based on the individual's needs and capability.

Hierarchy of objective and subjective measures for knee functional performance

When investigating the relationship between absolute scores of subjective and objective neuromuscular measures, KOOS (pain and quality of life sub-sections) had shown the most consistent correlation at 12 week post-surgery with objective measures of SMP, peak force and ATFD for quadriceps (injured legs) [r ranged between -0.32 to -0.46]. The negative small correlation implies that while there was improvements in the scores of the subjective outcome measure (e.g. KOOS pain and quality of life sub-sections), there was lack of improvement in the objective measures (e.g peak force for quadriceps) at 12 weeks post-surgery. Importantly the significant correlation observed between KOOS sub-sections and some objective neuromuscular measures might indicate the advantage that KOOS possesses over the other subjective functional measures due to the fact that it separates the scores of each sub-section. The absolute scores of K-SES and Lysholm shared the second position in terms of hierarchy of relationship with objective measures. For instance, K-SES had shown moderate correlation with RFD of hamstrings (injured leg); 0.44 and SMP of hamstrings [injured leg]; 0.42, $p<0.05$, while Lysholm had shown moderate correlation with measures of SMP for hamstrings [injured leg]; 0.45, $p<0.01$ and small correlation with peak force of hamstrings [injured leg]; 0.32, $p<0.05$. In comparison to quadriceps, hamstrings had shown significant correlation with the subjective measures of K-SES and Lyhsolm, suggesting that although the majority of participants had hamstrings graft, individual's perception towards the performance of hamstring musculature was not affected by the type of surgery performed. Interestingly no correlation between the absolute scores of objective and subjective measures had been found at the end point (24 weeks post-surgery) [$p>0.05$] of ACLR rehabilitation indicating that the relationship amongst objective and subjective measures was more effective in the acute phase of ACLR rehabilitation in comparison to the late phase of rehabilitation.

Change scores (i.e pre-surgery to 12 and 12 to 24 weeks post-surgery) of the outcome measures were also analysed in the current study to examine the clinical efficacy of accelerated conditioning both in the period of accelerated intervention and the in late phase of ACLR rehabilitation. It was expected in the current study that the extent of changes in the selected outcome measures (purported to be valid estimates of function according to the literature) would demonstrate appropriate correlation at pre-surgery or during the assessment occasions following ACLR surgery. When the change scores of objective and subjective outcome measures were analysed, KOOS and SMP (0.47), hop and Lysholm (0.46), hop (injured legs) and IKDC (0.43) and Lysholm and EMD (quadriceps injured leg) had demonstrated the highest correlation in the acute phase of rehabilitation (pre-surgery to 12 weeks post-surgery). Similar to the absolute scores, the correlation amongst the change scores of objective and subjective measures were small to moderate indicating that meaningful prediction models between the early change scores post-surgery in the objectively-measured and subjective outcomes of function would not be statistically feasible. There was no correlation between the change scores of ATFD and any objective or subjective measure of knee function. It is plausible that the latter finding supports the notion that for knee laxity assessments to be clinically more meaningful, an assessment beyond 6 months post-surgery is required in order to appropriately inform the knee functional status (Wojtys and Huston 2000).

It was interesting to note that the change scores of peak force for quadriceps had shown more consistent correlations with knee measures (with EMD, peak force, hop, Lysholm and IKDC) than hamstrings. For example, weak to moderate correlations between the change scores of EMD and peak force of quadriceps, and the functional measures of Lysholm, hop and IKDC (0.42, 0.35, and 0.32, $p<0.05$, respectively) had been observed at pre-surgery to 12 weeks post-surgery. This is in agreement with those findings reported in the literature (Beynnon et al. 2011, Risberg and Holm 2009, Liu-Ambrose et al. 2003). Although the studies of Beynnon et al. (2011) and Risberg and Holm (2009) were based on 2 years follow up, their studies might indicate that strength conditioning possesses superiority over proprioception and balance conditioning in the rehabilitation programme for ACLR, and that focus should be predominantly on strength rather than proprioception and balance conditioning for optimal outcome in the long term. This view was supported by the study of Cooper et al. (2005) who demonstrated that strength conditioning (bike, leg press, squat) in the first 6 weeks of ACLR rehabilitation offered more benefit than proprioception exercises, suggesting that the latter conditioning have superiority in the acute phase of ACLR rehabilitation. The lack of correlation between hamstrings and both the functional and subjective measures could be due to compromised strength of the latter muscles following the hamstring graft surgical procedure on most participants of this study (92%).

In contrast, although EMD and RFD are considered important neuromuscular factors that are required for generating functional movements, the change scores of the latter measures had shown small to moderate correlation with Lysholm and K-SES (0.42 and 0.34, $p<0.05$, respectively). These findings (small and poor correlations) highlight the importance of clinimetric utility of subjective measures (patient-reported outcomes) since individual's perceptions of capability are mis-matched against the objective outcome measures of function and neuromuscular performance. Therefore the effective and efficient management of ACLR rehabilitation would be compromised if progress is only monitored by patient-reported outcome measures. This might also support the argument that clinicians should not rely on one measure (be it objective or subjective) for determining the readiness and indeed the functional performance of knee.

Does early change of scores predict late change of scores?

The results revealed negative correlation ($r=-0.75$, $p<0.01$) in change scores of single leg hop (injured leg) between pre-surgery to 12 and 12 to 24 weeks post-surgery. It might be possible that the introduction of accelerated conditioning in the acute phase of rehabilitation (first 12 weeks post-surgery) had contributed to the negative relationship observed in the study. It is plausible that while increased improvement had taken place in the acute phase as result of increased frequency and intensity of exercise stress, the subsequent late phase had plateaued due to the discontinuation of accelerated rehabilitation. In addition, this pattern of negative correlation between early phase and late phases of rehabilitation had also been observed in the change scores of peak force quadriceps (-0.62, $p<0.01$). This also suggests that the increased rate of change (responsiveness) of the peak forces for quadriceps in the early stage (pre-surgery-12 weeks post-surgery) was followed by a lack of improvement (rate of change) in the late stage of rehabilitation (12- 24 weeks post-surgery).

On the other hand, small to moderate correlation were found between the early and late change scores of RFD and EMD for hamstrings (injured legs) [r= 0.36, 0.42, $p<0.05$, respectively]. These findings suggest that the latter components (EMD and RFD) had not been compromised amongst patients of hamstrings grafts (representing 92% of the sample of the current study). However, the magnitudes of correlation (early versus late change scores of RFD and EMD for hamstrings) are still clinically compromised ($r < 0.7$) to justify the use of accelerated intervention and subsequently the change of practice for ACLR rehabilitation.

The most notable result between the early change scores versus late change score of the outcome measures of knee was the lack of correlation in ATFD and SMP. The latter might indicate that early responses of patients (both in contemporary and accelerated groups) to the accelerated conditioning were not related to later dose-responses during ACLR rehabilitation. With regards to lack of correlation between the early and late change scores of knee laxity, Beynnon et al. (2011) had also reported similarity in increased knee laxity (anterior-posterior displacement of tibia relative to femur) at two years follow up in both the accelerated and non-accelerated rehabilitation groups (3.2 versus 4.5 mm, respectively, $p>0.05$) following ACLR surgery. Therefore it was within the expectation of the researcher of this thesis to observe no difference in knee laxity between the early and late phase of rehabilitation. Table 7.2 shows the key findings of study two (chapter five).

Key findings of study two	Objective versus subjective functional measures	Objective neuromuscular versus subjective measures	Hierarchy of measures with knee function	Early change scores versus late	Factors influencing outcomes
Were there any correlations amongst knee objective functional, subjective functional and objective neuromuscular outcome measures in ACLR clinical population?	Small to moderate correlations between absolute scores of objective functional and some subjective functional measures at 12 weeks post-surgery.	KOOS showed most consistent correlation (negative) with some objective neuromuscular measures, followed by K-SES and Lysholm as second most consistent.	Chang scores of KOOS and SMP, Lysholm and single leg hop showed the highest correlation at pre- to 12 weeks post-surgery but were not strong enough for feasible prediction model	Negative correlations in change scores of single leg hop (-0.75) and peak force of quadriceps (-0.62) at pre- to 12 weeks post-surgery	Small correlation between unstructured physical activity and single leg hop (0.33) at pre-surgery to 12 week post-surgery.

Table 7.2: key findings of study two (chapter five).

Anthropometrics and orthopaedic-related factors influencing knee function following ACLR surgery and rehabilitation

The purpose of investigating the relationship between factors such as unstructured physical activity and the outcome measures of knee function was to establish the fact that the latter factor had contributed on the results of outcome measures of knee function following ACLR rehabilitation. Previous study (study one, chapter four) had demonstrated that orthopaedic-related factors such as waiting time, and unstructured physical activity and body mass were influential on the outcomes of ACLR rehabilitation. The current study had also shown a significant correlation between the change scores of unstructured physical activity and single leg hop (injured leg) [($r=0.33$, $p<0.05$)] at pre-surgery to 12 week post-surgery. However, this imply that although significant correlation had been observed amongst the latter outcomes, this correlation was considered “insufficient” to offer clinical relevance or predict which measures are important predictors for optimal knee function as coefficient of determination (r^2) would suggest less than 10% of the shared variance between outcomes measures. The results of the current study supports the notion that for the purpose of evaluating post-surgical outcomes, current practice of ACLR rehabilitation as well as future research should emphasise on investigating the concurrent use of functional, neuromuscular and patient-reported measures. In summary, the lack of robust and more prominent linkage amongst objective and subjective functional, and objective neuromuscular indices indicate that, while all the outcomes measures had shown sufficient validity and reproducibility characteristics, the latter outcomes have a separate individual contribution in determining the important aspects of knee functional capability.

C) Did ACE I/D gene polymorphism and its genotypes have any influence on the responsiveness to strength training and the knee outcomes in ACLR clinical population?

Angiotensin-converting-enzyme (ACE) gene is one of the genes that play an important role in circulating human renin-angiotensin system as well as being a regulator of muscular hypertrophy. To date, the gene-environment interaction between candidate genotypes of gene polymorphisms and the rate of strength gain (responsiveness to strength intervention) is still largely understudied (Beunen et al. 2010, Pescatello et al. 2006). ACE I/D gene polymorphism has also been significantly associated with response to training (Colakoglu et al. 2005, Pescatello et al. 2006, Giaccaglia et al. 2008, Folland et al. 2000). The systematic review in chapter three revealed that of eight studies that investigated the influence of ACE I/D polymorphism on responsiveness to training, only four studies (Colakoglu et al. 2005, Pescatello et al. 2006, Giaccaglia et al. 2008, Folland et al. 2000) had shown that D alleles of ACE I/D polymorphism demonstrated greater strength gains compared to I alleles (percentage range of strength gains in all four studies was 14.3% to 38 %; Cohen d = 0.07 to 2.00). However no previous study had examined the influence of ACE I/D gene polymorphism on responsiveness to strength or rehabilitative training intervention.

Study three:

Are patients with the D allele group more responsive to rehabilitative training than those with the I allele?

Of the 5 outcome measures analysed [the objective functional (single leg hop) and objective neuromuscular outcome measures (peak force, EMD, RFD, SMP for quadriceps and hamstrings)], change scores of peak force of quadriceps had shown statistically significant interaction using 3 way factors (ACE genotypes [DD, ID, II] time [pre-surgery (0), 12 and 24 weeks post-surgery], leg [injured, uninjured]) with superiority of strength gains (responsiveness) between the period from 12 to 24 weeks post-surgery favouring the DD and ID over II genotype group. Interestingly, at 12 weeks post-surgery, when the results of the current study had been compared with a previous study in the literature (Folland et al. 2000) who introduced 6 weeks strength intervention, the percentage change scores of peak force for quadriceps in the current study (98.4 and 64.9) were higher than those reported in the latter study (32.5 and 9%) for D and I allele, respectively. It is plausible that patients in the current study had experienced deconditioning due to the surgical intervention (ACLR surgery) thus demonstrated quicker recovery rate in the peak forces of quadriceps during ACLR rehabilitative training when compared to the healthy population in the study of Folland et al. (2000). The 15% advantage of peak force for quadriceps that is attributable to ACE D allele might possibly justify the rationale for changing the delivery of rehabilitative care as patients with the D allele demonstrated better response to rehabilitative training. Therefore, the 15% advantage favouring the D allele group might suggest that strength training can be possibly prescribed routinely earlier to patients carrying the latter allele.

On the other hand, there was a lack of significant interaction using 3 way factors (ACE genotype by leg by time) and 2 way factors on the change scores of outcome measures of single leg hop (objective function outcome measures) and peak force, EMD, RFD, SMP and ATFD (objective neuromuscular outcome measures). The lack of significant interaction on the latter outcome measures might be due to the fact that the specific types of rehabilitation incorporating accelerated conditioning within the current study had endorsed the improvement of muscle strength status rather than the patient's functional status (single leg hop), reaction time (EMD), force generation (RFD) and muscle re-education following ACL injury disruption (SMP).

What is the relative influence of ACE I/D gene polymorphism on the responsiveness of outcomes amongst patients who had undergone accelerated and contemporary rehabilitation conditioning following ACLR surgery?

The secondary aim of the current study was to investigate the relative influence of ACE I/D genotypes on the responsiveness of outcomes amongst patients who had undergone accelerated and contemporary rehabilitation conditioning following ACLR surgery. Anthropometric factors including waiting time, body mas and unstructured physical activity had an influence on the outcome measures of knee function following ACLR rehabilitation had been found to be influential (significant interaction using 3 way factors [group by leg by time] ANCOVA in the peak force and EMD of hamstrings) in study one (chapter four). However, when the ACE I/D genotypes had been statistically adjusted, the current study (study three) had shown similar pattern of improvement (no significant interaction of group (accelerated; contemporary) by leg (injured, uninjured) by time (pre-surgery, 6, 12 and 24 weeks post-surgery) in both the accelerated and contemporary groups for the change scores of peak force of quadriceps in the injured and uninjured legs over time. The current study indicates that ACE I/D genotypes was not an influential factor on the objective functional (single leg hop) and objective neuromuscular outcome (peak force, EMD, RFD, SMP and ATFD) measures. Similar pattern of non-significant interaction was had also been noted on two way factors (group by time), suggesting that the two groups had not been differentially influenced by the injured and uninjured legs. The researcher of this thesis acknowledges the fact that study three was an exploratory study and that the physical activity and responsiveness to physical training phenotype is a complex trait. This view was supported in the literature by Eynon et al. (2011) and Hand et al. (2007) who claimed that the effect of single gene variant in the context of responsiveness to exercise training is small. It was the intention of the researcher of this thesis to incorporate several gene polymorphisms (ACTN3 R577X, insulin-like growth factor I protein IGF1 repeat promoter polymorphisms) in the investigation of responsiveness to rehabilitative training within the clinical population. However due to limited resources and logistical feasibility for the current research this was deemed not possible.

Therefore, examining more than one gene polymorphism in order to fully understand the true response of individuals to rehabilitative training should be the focus of future studies. However, the current has provided some evidence to suggest that rehabilitative care for clinical population with ACLR surgery might be changed on the basis that patients with the D allele genotype of ACE I/D polymorphism are more responsive to strength training thus could be influential in optimising the objective neuromuscular outcomes of knee following ACLR surgery. Table 7.3 shows a summary of the key findings of study three (chapter six).

Key findings of study three	**ANOVA (ACE I/D by leg by time)**	**ANCOVA (group by leg by time)**
Did ACE I/D gene polymorphism and its genotypes have any influence on the responsiveness to rehabilitative training and the knee outcomes in ACLR clinical population?	Greater improvement in change scores of peak force for quadriceps in accelerated group at pre-surgery to 12 weeks post-surgery and percentage change of 15% in D allele group	No significant interaction in change scores of any outcome measures at any period of formal ACLR rehabilitation.

Table 7.3: Key findings of study three (chapter six).

7.1.1 Limitation of the studies of the thesis

Study one (chapter four) and study two (chapter five)

- Patient's progression from one phase of ACLR rehabilitation to another should be based on achieving certain goals in each phase of rehabilitation (De Carlo and McDivitt 2006). The progression in this study (i.e. increased dosage of accelerated conditioning) however was based on clinical reasoning (i.e. if they had attained full weight bearing, full ROM and isometric OKC quadriceps in the acute phase of accelerated rehabilitation. This was achieved as previously mentioned earlier (study one, chapter two) by verifying the successful manipulation of treatment check that included early ROM, weight bearing and isometric OKC quadriceps in the accelerated group. However, although data from patient's diary that were used to assess compliance didn't suggest that patients had struggled to follow the prescribed programme, it is possible that some patients were not satisfied to progress to the next phase of rehabilitation. Future studies evaluating patient's physical and psychological progression at each phase of rehabilitation might contribute to understand the potential factors that determine patient's progression in ACLR rehabilitation. Mendonza et al. (2007) had shown that motivation and self-efficacy factors had positive association with rehabilitation outcomes and patient's compliance.

- Study one (chapter four) had not considered the pre-operative rehabilitation phase of ACLR injury. The Methodist Sports Medicine Centre rehabilitation protocol (introduced by De Carlo and McDivitt in 1986) had emphasised on the importance of pre-operative rehabilitation for better management of swelling and restoration of ROM before the surgery. The latter authors reported high correlation between swelling control and improved ROM before surgery and the early restoration of ROM and strength following surgery. It might be speculated, therefore, that the lack of this phase might have contributed to some of the poor findings demonstrated in some of the outcome of the trial.

- Due to lack of consensus within the literature on the definition of "accelerated rehabilitation", the investigator of study one (chapter four) was not able to include all the accelerated exercises prescribed in previous robust studies (chapter two).

Study three (chapter six):

- The study had not achieved the minimal estimated sample size (n=50) to detect phenotype differences between the genotype groups. Therefore, the proportion of variance attributable to ACE genotypes would therefore be deemed very small and the analysis of this study should be considered exploratory.

- The effect of single gene variant in this context is small given that the physical activity phenotype is a complex trait

7.1.2 Recommendation and future direction

Study one (chapter four) had not included pre-operative rehabilitation phase as part of the rehabilitation programme of "accelerated rehabilitation". The current trend of accelerated rehabilitation is to incorporate pre-operative rehabilitation for better management of knee swelling and improved ROM before surgery (De Carlo and McDivitt 2006). Therefore future studies could enhance the understanding and contribution of pre-operative rehabilitation phase towards successful outcomes of ACLR rehabilitation. To the knowledge of the author, no published study had assessed the outcome measures associated with pre-operative rehabilitation of accelerated programme. Therefore future studies could enhance the understanding and contribution of such rehabilitation in the successful outcomes of ACLR rehabilitation. With respect to correlation of knee outcome measures, clinicians and therapists should be cautious on progressing and planning their rehabilitative regime based on one particular measure only. While contemplating the predominantly weak to moderate associations linking conventional result measures and functional performances displayed, no sole result measure should be regarded as ultimate for the assessment of intervention subsequent to ACL damage, and clinical result measures only are regarded as inadequate in establishing the readiness of the athlete to go back to competitive sport. The results of the current studies of this thesis support the notion that for the purpose of evaluating post-surgical ACLR outcomes, current practice of ACLR rehabilitation as well as future research should emphasise on investigating the concurrent use of functional and neuromuscular outcome measures. The latter outcomes should be treated as equally important components towards achieving optimal outcomes of knee function following ACLR surgery. With regards to the influence of ACE I/D polymorphism, several gene polymorphisms had been shown to contribute to the differential response to strength training and ACE I/D polymorphism is one of them. As suggested by Eynon et al. (2011), the effect of single gene variant in the investigation of the influence of complex phenotype such as physical performance is small. Therefore, future studies might usefully focus on examining more than one gene polymorphism in order to understand the true response of individuals to strength and rehabilitative training.

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Appendices

Queen Margaret University EDINBURGH & The Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust

I. Appendix: Patient Information Sheet

PROJECT TITLE

FUNCTIONAL AND PHYSICAL RESPONSIVENESS ASSOCIATED WITH ACCELERATED CONDITIONING AND GENE POLYMORPHISM FOLLOWING

Researchers: Abdulhameed Alkitani (Chief Investigator)

Prof. Nigel Gleeson (Professor in Exercise and Rehabilitation Science)

Mr. Dai Rees (Consultant Orthopaedic Surgeon)

Dr. Fiona Coutts (Senior Physiotherapist, Dean of the School of Health Sciences)

Mr. Simon Roberts (Consultant Orthopaedic Surgeon)

Andrea Bailey (Clinical Specialist Physiotherapist)

PARTICIPANT INFORMATION SHEET

You are being invited to take part in the above titled research study. Before you decide to participate, it is important for you to understand why this research is being carried out and what it will involve. Please take your time to read the following information sheet and please feel free to ask any questions if there is anything that is not explained clearly. If you would like more information, please contact the research team (contact details are provided at the end of this information sheet).

Part 1 tells you the purpose of this project and what will happen to you if you take part.

Part 2 give you more detailed information about the conduct of the project.

Part 1:

WHAT IS THE PURPOSE OF THE STUDY?

This study is part of a doctoral research programme that is currently being undertaken at Queen Margaret University, Edinburgh. The purpose of this study is to test the effectiveness of rehabilitation involving an especially accelerated approach to rehabilitation and compare this technique to the normal rehabilitation programme that is currently being used at Robert Jones & Agnes Hunt Orthopaedic Hospital (RJAH), Oswestry. In addition, the study will investigate very specifically the type of genes that you might have which are thought to control how well you respond to physical training. Studies have shown that people with particular genes tend to respond better to exercises. This rehabilitative programme is detailed in the anterior cruciate ligament surgery and rehabilitation patient advice booklet you have already received. This information guide provides you with examples of the physiotherapy programme that includes strength, endurance and other related techniques used within the field of physiotherapy.

WHY HAVE I BEEN CHOSEN?

In this study, the research team will be investigating patients (like yourself) who have elected to undergo anterior cruciate ligament reconstruction knee surgery and who are otherwise medically fit. The reason you are being invited to take part in this study is that you fit this description.

DO I HAVE TO TAKE PART?

Participation in this study is entirely voluntary and you are free to decline participation or to withdraw from the study at any time. If you do decide to withdraw, you will not need to give any reasons and will continue your rehabilitation as normal with no prejudice.

WHAT WILL HAPPEN TO ME IF I TAKE PART AND WHAT WOULD I HAVE TO DO?

> The research team would like to find out, whether or not the current way of rehabilitating patients who have had your type of surgery can be improved upon. To do this, the research team will put participants into groups that will each experience a different style of rehabilitation. The results will be compared to see which one, if any, is most beneficial. You will be randomly selected (by chance) into one of two groups. It is important to note that no matter which group you are allocated into, you will receive the same standard of care and rehabilitation that is routinely implemented as part of your physiotherapeutic treatment. In addition we will look at participant's genes (DNA) and proteins and compare them between the two rehabilitation groups.

This will help us identify which of these genes help us understand the key areas of successful rehabilitation outcomes.

WHAT WILL YOU DO WITH MY BLOOD SAMPLES (DNA)?

The study will investigate the type of genes you express which are thought to respond to physical training. A blood sample will be taken from each participant to find out whether the improvement shown through different stages of rehabilitation is genetic- related or not. The standard technique for taking blood would be used. You might experience brief discomfort; some people also experience brief pain or dizziness when giving blood. We will take a blood sample of 10 ml (about 2 teaspoonfuls) during your last orthopaedic clinic visit prior to surgery or during the surgery. The volume we need is much less than a tenth of that taken from a Blood Donor. All blood samples will be initially stored in a secure place in a freezer at -20 degree temperature at RJAH Hospital, Oswestry, England and will then be transported by car to Napier University, Edinburgh, Scotland for analysing biological markers for 2 particular genes that are thought to be responsive to physical training (target genes). No other tests whatsoever will be performed on the samples taken for this project.

Throughout your rehabilitation programme you will be attending the physiotherapy clinic approximately 15–20 times over the 24 week rehabilitative period. However, if you cannot attend for whatever reason, the research team might contact you by email, letter or telephone to discuss your rehabilitation progress. You will be asked to complete questionnaires during your scheduled physiotherapy appointment. This will take no longer than 3 minutes to complete typically (up to 15 minutes in the first session because the research team will explain about any questionnaire needing completion).You also will need to attend up to four assessment sessions (approximately one hour per session) and will take place on a day that you would normally attend the physiotherapy clinic. Your first appointment for assessment will be prior to your surgery. You will be assessed typically when you visit hospital for your routine outpatient check-ups at 6 weeks, at 12 weeks, and 24 weeks following surgery. Within these sessions, you will be tested using advanced computerised data acquisition software. We will be monitoring aspects of knee joint performance such as:

(1) The strength of your leg muscles and your ability to repeat brief strength tasks accurately.

(2) How quickly your leg muscles can react to a brief and painless magnetic pulse.
(3) The laxity/looseness of your knee will also be tested.
(4) The type of relationship between the above performance indexes and the type of genes expressed by you.

You will also be asked to keep a weekly diary of your rehabilitation (should take no longer than 10 minutes per week to complete) and recorded over the 24-week period.

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISKS, AND WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

No matter which rehabilitation group you are allocated into, there will be no extra clinical risks or disadvantages to yourself. This is because all participants in this study will be performing the same exercises at different stages of the rehabilitation programme. In addition, taking part might be more beneficial to your recovery, and the information the research team gathers from this study might inform and improve future clinical practice.

WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

The research findings may inform the research team that one way of rehabilitating patients is better than another. This will then alter the way the physiotherapy team suggest patients rehabilitate in the future. If you wish, after the research is complete, we can disseminate the findings from the study to you. The findings may also be written and published in medical/scientific journals to aid other clinicians and patients elsewhere.

WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

The research team will keep your name, age, sex and your results in a record that will be stored on a password-protected computer to ensure only persons involved in the study can access the information. The storage and subsequent destruction of your data is compliant with the Data Protection Act 1998. All information that is collected about you will be kept strictly confidential. Any information about you that leaves this hospital will have your name and address removed and will subsequently be anonymous.

<u>COMPLAINTS</u>

If you believe you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through the Queen Margaret University, Edinburgh and RJAH, Oswestry, who are acting as the research sponsors. Details about this are available from the research team. Also, as an NHS patient, you have the right to pursue a complaint through the usual NHS complains procedures. Please note that the NHS has no legal liability for non-negligent harm. However, if you are harmed as a result of someone's negligence, you may have grounds for legal action against the NHS, but you may have to pay your legal costs.

Part 2:

<u>CAN I WITHDRAW FROM THE PROJECT AFTER SAMPLES HAVE BEEN TAKEN?</u>

Yes, if you choose to withdraw after having given a sample, just contact the research staff. You won't have to give a reason and your blood and DNA samples, data and any personal identifiable information will be destroyed. However we would not be able to destroy samples and non-identifiable data which had already been processed and analysed.

<u>WILL TAKING PART IN THE PROJECT AFFECT MY ABILITY TO GET INSURANCE?</u>

No. This project does not perform a "genetic test" as identified by insurance companies and your taking part in this project will have no effect on your eligibility for insurance.

WHAT WILL HAPPEN TO THE SAMPLES AND INFORMATION?

The blood samples will later on be disposed (destroyed) in accordance with the Human Tissue Authority Code of Practice.

WILL I GET ANY FEEDBACK ON THE RESULTS OF GENETIC TESTS?

No. All genetic tests will be anonymous. Furthermore the results of single genetic tests will not have any proven value for clinical care of people who take part in this project.

WHO HAS REVIEWED THE STUDY?

For you to have been offered participation in this study, it will have had to have been already given a favourable ethical opinion for conduct in the NHS by the Staffordshire Local Research Ethics Committee and by Queen Margaret University Edinburgh's local Ethics Committee. It will also have been approved for scientific merit by the Research Panel at Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry. If you would like some independent advice about whether you should take part in the study, please contact:

Prof. Tom Mercer

Professor of Exercise Physiology and Rehabilitation

School of Health Sciences

Queen Margaret University, Edinburgh

Musselburgh

United Kingdom

EH21 6UU

E-mail: tmercer@qmu.ac.uk

Tel: +44 (0) 131 474 0000

CONTACT DETAILS FOR FURTHER INFORMATION:

We hope you will participate in this study, but if you have any questions or would like more information, please contact:

Abdulhameed Alkitani	Andrea Bailey
Chief Investigator, Research Team.	Clinical Specialist Physiotherapist
School of Health Sciences	Physiotherapy Department
Queen Margaret University, Edinburgh	RJAH Orthopaedic & District NHS Trust
Musselburgh	Oswestry
United Kingdom	SY10 7AG
EH21 6UU	TEL: 01691 404160
MOBILE: 07736968531	E-mail: andrea.bailey@rjah.nhs.uk
E-mails: aalkitani@qmu.ac.uk	

II. Appendix: Informed Consent Form

Queen Margaret University EDINBURGH & **The Robert Jones and Agnes Hunt Orthopaedic and District Hospital** NHS Trust

School of Health Sciences
Queen Margaret University Drive
Musselburgh
East Lothian
EH21 6UU

National Centre for Sport Injury Surgery
Gobowen
Oswestry
Shropshire
SY10 7AG

PROJECT TITLE:
FUNCTIONAL AND PHYSICAL RESPONSIVENESS ASSOCIATED WITH ACCELERATED CONDITIONING AND GENE POLYMORPHISM FOLLOWING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

RESEARCHERS & COLLABORATORS:

Abdulhameed Alkitani (Chief Investigator/PhD. Candidate)
Mr. Dai Rees (Consultant Orthopaedic Surgeon)
Mr. Simon Roberts (Consultant Orthopaedic Surgeon)
Andrea Bailey (Clinical Specialist Physiotherapist)
Pro. Nigel Gleeson (Professor in Exercise and Rehabilitation Science)
Dr. Fiona Coutts (Senior Physiotherapist, Dean of the School of Health Sciences).

CONSENT FORM

Please initial box

1. I confirm that I have read and understand the information sheet provided for the above study. ☐
2. I have had the opportunity to consider the information, ask any questions, and have had these answered satisfactorily. ☐
3. I understand that my participation in this study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that the study will involve giving a blood sample for DNA extraction and for analysis in a laboratory examining differences in biological molecules. ☐
5. I understand that the study will involve secure storage of my health information in databases and of de-indentified specimens of my biological samples. ☐
6. I understand that data collected during this study may be looked at by responsible individuals from the NHS (being Robert Jones and Agnes Hunt Orthopaedic & District Hospital, Oswestry) and Queen Margaret University throughout the course of this study. ☐
7. I agree that the research team/physiotherapists may contact me by email, letter or telephone to discuss my rehabilitation progress should this be needed. ☐
8. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

If you would like some independent advice about whether you should take part in the study, please contact:

Prof. Tom Mercer
School of Health Sciences
Queen Margaret University, Edinburgh
EH21 6UU
E-mail: tmercer@qmu.ac.uk Tel: +44 (0) 131 474 0000

Version2/ Alkitani/1-2-2012

III. Appendix: NHS Ethics Committee Approval

NHS
Health Research Authority
NRES Committee West Midlands - Staffordshire
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7831
Facsimile: 0161 625 7299

13 April 2012

Mr A Alkittani
Senior Sports Physiotherapist
37 Radbrook Hall Court
Shrewsbury
SY3 9AF

Dear Mr Alkittani

Study title:	**Investigation of the Effects of Accelerated Rehabilitation and Genetic Influence on Functional, Neuromusculoskeletal and Psychophysiological Performances in patients with Anterior Cruciate Ligament Reconstructive Surgery.**
REC reference:	**11/WM/0417**

Thank you for your letter of 20 February 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Committee held on 11 April 2012. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of insurance or indemnity		29 July 2011
Investigator CV		22 November 2011
Other: Summary CV for supervisor - Professor Gleeson		01 March 2011
Other: Summary CV for supervisor - Dr Coutts		06 April 2011
Other: A comparison of 'Contemporary' and 'Accelerated' rehabilitation programmes	1	25 November 2011
Participant Consent Form	1	25 November 2011
Participant Consent Form	2	01 February 2012
Participant Information Sheet	1	25 November 2011
Participant Information Sheet	2	01 February 2012
Protocol	1	25 November 2011
Questionnaire: The Performance Profile (validated)		
Questionnaire: SF-36 Health Survey (validated)		
Questionnaire: Seven-Day Physical Activity Recall (validated)		
Questionnaire: 2000 IKDC Knee Forms (validated)		
REC application	IRAS 3.2	23 November 2011
Referees or other scientific critique report		28 October 2011
Response to Request for Further Information		20 February 2012
Summary/Synopsis	1	25 November 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

11/WM/0417	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

L Brown

pp. **Dr Kathryn Kinmond**
Chair

Email: laura.brown@northwest.nhs.uk

Enclosures:	List of names and professions of members who were present at the meeting "After ethical review – guidance for researchers"
Copy to:	Professor N Gleeson, Professor In Exercise & Rehabilitation Sciences, Queen Margaret University Edinburgh Miss T Jones, Research Governance Facilitator, Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Trust

A Research Ethics Committee established by the Health Research Authority

IV. Appendix: Research and Development Robert Jones and Agnes Hunt Orthopaedic Hospital

The Robert Jones and Agnes Hunt **NHS**
Orthopaedic Hospital
NHS Foundation Trust

Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust
Oswestry
Shropshire
SY10 7AG

Tel: *01691 404575*
Fax *01691 404112*

STRICTLY PRIVATE & CONFIDENTIAL
Mr Abdulhameed Alkitani
37 Radbrook Hall Court
Shrewsbury
SY3 9AF

23 May 2012

Dear Abdulhameed

Letter of Access for Research

This letter confirms your right of access to conduct research through The Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Foundation Trust (RJAH) for the purpose and on the terms and conditions set out below. This right of access commenced on the 1st March 2012 and 1st June 2013 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at RJAH has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to RJAH premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through RJAH, you will remain accountable to your employers, Queen Margaret University but you are required to follow the reasonable instructions of Mrs Teresa Jones in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with RJAH policies and procedures, which are available to you upon request, and the Research Governance Framework.

V. Appendix: RJAH Rehabilitation for ACLR

PHASE OF REHABILITATION	STAGE OF REMODELLING	'CURRENT'	PURPOSE/ AIM	'PHASED-STRENGTH & ENDURANCE'	ETHICAL CONSIDERATIONS
PHASE 1 Day 1-Discharge	The graft is at its strongest at this stage, with respect to the soft tissue.	• Continuous Passive Motion (C.P.M.) machine as directed by physiotherapist. • Cryocuff/ Ice. • Patella mobilisations. • End of range extension mobilisations mobilisations as directed by physiotherapist. • Hamstring (H) and calf stretches. • Ankle exercises. • Passive F over edge of bed. • Static quadriceps (Q). • Co-contraction Q and H. • Avoid 'heavy' eccentric (ecc) Q, which may overload the harvest site. • Prone H, concentric (con)/ecc/isometric (isomet). • Prone straight leg raise (SLR). • Partial weight bearing (PWB) with elbow crutches to comfort. • Cricket splint insitu for first week to reduce haemorrhage and prevent intracondylar notch scarring. Can be removed for exercises and sleep. • Mini squats. • Heel raises. • Weight transferring. *PLEASE REFER TO APPENDIX 11 (A description of programmes of exercise used in 'current' practice for rehabilitation associated with ACL-reconstruction) FOR DETAILS*	Reduce inflammation. Gain full terminal extension (E). Promote distal circulation. Gradually regain range of motion (ROM) Introduce early Quadriceps (Q) and Hamstring (H) work. Promote early mobility.	As traditional	The exercises, duration of each exercise session and the physiotherapists time is the same as the traditional. The various strength/ endurance exercises are performed concurrently in the traditional programme. The strength/ endurance emphasis separates the strength/ endurance work, where clinically possible. Thus a non-concurrent rehabilitation programme will be followed. Consequently, the overall administration of the traditional programme is 'packaged' differently.

PHASE OF REHABILITATION	STAGE OF GRAFT REMODELLING	'CURRENT'	PURPOSE/ AIM	'PHASED-STRENGTH & ENDURANCE'	ETHICAL CONSIDERATIONS
PHASE 2 Discharge – 10 Days **IDEAL CRITERIA BEFORE COMMENCING** • Full active and passive Extension • Mobilise independently +/- walking aids	No initial blood supply to graft, results in avascularisation of the soft tissue aspect.	• Static bike no/low resis. as directed by physiotherapist. • Gradually increase weight bearing. • Gait re-education (wean off splint and elbow crutches). • Low step-touch→step up. • Active open kinetic chain (OKC) Q 90°-45°. • Progress H work re: Repetitions (Reps)/Resistance (Resis), as directed by the physiotherapist. • Other muscle groups not to be neglected.	Promote early function. Increase ROM Encourage weight bearing. Improve muscular strength/ endurance and control.	As traditional	

PHASE OF REHABILITATION	STAGE OF GRAFT REMODELLING	'CURRENT'	PURPOSE/ AIM	'PHASED-STRENGTH & ENDURANCE'	ETHICAL CONSIDERATIONS
PHASE 3 Day 10 – Week 6 **IDEAL CRITERIA BEFORE COMMENCING** • Minimal discomfort. • SLR with no lag. • Active range of motion (AROM) = Full E → approx. 100° F	Avascularisation of graft leads to continual decrease in graft strength. The graft becomes enveloped in a synovial sheath.	• Full weight bearing (FWB). • Gait with predictable changes in direction. • Prone auto-overpress F →develop Q stretch • Step ups (for/back/sideways) →height/reps/resis/ speed. *Eg. 10x slow pace, 10x fast pace.* • Leg press →reps/resis/speed. *Eg. 2 x 10 Reps (10 Rep Max)** • Early plyometrics. • Rowing →dist/speed/resis. *Eg. Resis 3 (Concept II setting)**, 1500m Dist., x 10 min* • Progress proprioception →wobble boards/sit-fit/trampette/crash mats/etc. • Gym ball, Theraband work • Hydrotherapy/swimming (AVOID breaststroke legs until 3 month stage) • Progress general leg exercises VMO, ab/adduction,gluteals, etc. • Upper body. • Muscle balance as appropriate. • Flexibility as appropriate. DURING EACH SESSION THE PHYSIOTHERAPIST DIRECTS RESISTANCE, REPETITIONS AND SPEED OF EACH EXERCISE TO PROMOTE STRENGTH, POWER AND ENDURANCE ie CONCURRENT TRAINING.	Progress functional activities. Prevent anterior knee pain. Prevent scar adherence. Prevent joint stiffness. Restore normal gait pattern. Promote appropriate muscle strength/ power and endurance. Improve proprioception. Maintain cardiovascular fitness. Encourage patient compliance.	As traditional, except alternate blocks of to separate strength and endurance work. Each block to be separated from the other by at least 2 days of rest/ maintenance. **Strength** Step ups (forwards and sideways) holding dumbbells, 6 – 10 kg total x 5 Reps. Leg Press 3 x 5 Reps (Weight = 5 Rep Max) Rowing Resis. 8, 1000m Dist., x 6 min General leg and upper body weights set at 3 –5 Rep Max. **Endurance** Step ups (forwards and sideways) body weight only x 20 Reps. Leg Press 2 x 20 Reps (Weight = 20 Rep Max) Rowing Resis. 2, Dist. 2200m x 15 min General leg and upper body weights set at 20 Rep Max.	

**Rep Max = Maximum number of repetitions a particular weight can be lifted in a controlled manner (i.e. 10 Rep Max = a weight that can be lifted ten times, but is too heavy to lift an eleventh).*
***Concept II = An indoor rowing machine.*

STAGE OF REHABILITATION	STAGE OF GRAFT REMODELLING	'CURRENT'	PURPOSE/ AIM	'PHASED-STRENGTH & ENDURANCE'	ETHICAL CONSIDERATIONS
PHASE 4 From Week 6 – 12 **IDEAL CRITERIA BEFORE COMMENCING** • 'Normal' gait pattern, pain free. • Full ROM • 1 leg balance ~1 min.	Bone blocks unite with surrounding bone and vasculrisation of the graft commences. An increase in graft laxity is usually apparent on testing between ~ week 10 – 12.	• Progress above as able. • Trampette jogging. • Treadmill walking. →duration/incline/ decline/cadence. • Isokinetic H.	Continue to promote specific function. Increase muscle work and control through range Isomet. Q strength = 75 –85%	**Maintenance level during Strength block** Treadmill walk 7 min duration, Walk x 1 min → Fast walk level x 1 min → Fast walk alternate 30 sec 5%, 30 sec 10%, 1 min level (x 4 min Total) → Walk x 1 min **Stength** Isokinetic H, 2 x 3 Reps at 60° **Endurance** Treadmill walk 11 min duration, Walk x 2 min → Moderate pace walk level x 2 min → Moderate walk 2 – 5% incline x 5 min → Moderate walk level x 1 min → Walk x 1 min Isokinetic H, 1 x 20 Reps at 180°	

PHASE OF REHABILITATION	STAGE OF GRAFT	'CURRENT'	PURPOSE/ AIM	'PHASED-STRENGTH & ENDURANCE'	ETHICAL CONSIDERATIONS
PHASE 5 From Month 3 **IDEAL CRITERIA BEFORE COMMENCING** • 30 min. fast walk. • Row 2000m within 15 min., moderate resistance. • H ~90% of contra-lateral side. • Adequate dynamic proprioception	By month 4 complete re-vascularisation with the laying down of collagen occurs. A gradual increase in strength is gained as the graft remodels.	• Isokinetic Q. *E.g. 2 x 3 Reps 60°, 2 x 10 Reps 180°, 10 – 20 sec Recovery* • OKC Q →reps/resis/speed/con/ ecc/isomet. *E.g. F/E 2 x 5 Reps (5 Rep Max), 1 x 3 Ecc Q* • Plyometrics, drops from 6-18"/ bounding, etc. • Hopping →stride/direction/stops/ speed. • Jogging →Running Surface/distance • Progress to incorporate: Agility, run/ sprint/cut/ pivot/ accelerate/ decelerate. *Surface = Sprung floor/ Grass/ Track X 10 min Randomised*	Bias to specific function/ sport.	**Strength** Isokinetic Q, 2 x 3 Reps at 60° OKC Q, F/E 3 x 3 Reps (3 Rep Max) Ecc. Q, 2 x 3 Reps at (5 Rep Max) **Maintenance level during Strength block** T.mill Jogging 8 min duration, Walk x 1 min → Light jog x 1 min → Alternate 1 min jog/ 1 min light jog (x 5 min total) → Walk x 1 min Running (Surface = T.mill/ Track/ Grass) 15 min duration, 1 min Light jog → 2 min Jog → Alternate 1 min Run/ 30 sec Sprint x 10 min Total → Jog x 1 min → Light jog/ Fast walk x 1 min **Endurance** Isokinetic Q, 1 x 20 Reps at 180° OKC Q, F/E 2 x 20 Reps (20 Rep Max) Ecc. Q, 1 x 10 Reps (15 Rep Max) T.mill Jogging 12 min duration, Walk x 2 min → Light jog x 2 min → Jog x 5 min → Light jog x 2 min → Walk x 1 min Running (Surface = T.mill/ Track/ Grass) 20 – 30 min duration, 1 min Light jog → 2 min Jog → 10 - 20 min Run → 5 min Jog → 2 min Jog	

PHASE OF REHABILITATION	STAGE OF GRAFT REMODELLING	'CURRENT'	PURPOSE/ AIM	'PHASED-STRENGTH & ENDURANCE'	ETHICAL CONSIDERATIONS
PHASE 6 From Month 5 **IDEAL CRITERIA BEFORE COMMENCING** • Dependent on sport. • 80-90% isometric and isokinetic Q strength of contra-lateral side. • Proprioception ~90% contra-lateral side.		• Non-contact training. *Sport specific 1 – 2 hr duration combining strength and endurance where applicable for particular sport.* • Non-contact sport.	Prepare physical and psychological ability for complete return to unrestricted function.	Non-contact training. Sport specific, with set time durations. Separating strength and endurance work (except maintenance levels) by at least 24 hrs.	
PHASE 7 From Month 6 **IDEAL CRITERIA BEFORE COMMENCING** • Symptom free training. • No residual complications. • Psychologically prepared.	Gradual organisation of collagen. At 1 year the graft resembles the appearance of a ligament with densely organised bundles. Graft strength is thought to range from 30-60% of the original. The laxity of the graft appears to be linked with muscle strength.	• Earliest return to contact sport.	Unrestricted confident function.		

VI. Appendix: Clinimetric Qualities (Reliability and Reproducibility)

	pre-op				6th week				12th week				24th week			
	ICC		SEM%		ICC		SEM%		ICC		SEM%		ICC		SEM%	
variables	inj	ninj	inj	ninj	inj	ninj	inj	ninj	inj	ninj	inj	ninj	inj	ninj	inj	ninj
emdh	0.46	0.88	9.5	7.9	0.51	0.78	8.2	7.9	0.44	0.74	6.6	6.9	0.53	0.81	8.9	6.3
emdq	0.73	0.78	10.1	8.3	0.71	0.67	8.7	8.1	0.62	0.59	7.9	7.7	0.64	0.68	10.1	8.4
hop	0.92	0.91	6.0	6.3					0.91	0.92	6.8	5.8	0.92	0.94	5.9	4.9
lax	0.71	0.84	10.0	13.1	0.73	0.61	22.2	21.0	0.58	0.55	19.0	22.9	0.71	0.52	16.0	20.6
pfh	0.97	0.99	5.3	2.7	0.98	0.99	5.3	2.7	0.92	0.99	8.6	2.7	0.93	0.98	7.7	3.8
pfq	0.96	0.96	5.6	4.5	0.95	0.96	7.4	4.9	0.94	0.95	7.0	5.2	0.96	0.93	5.6	6.0
rfh	0.81	0.71	28.5	36.9	0.75	0.46	40.9	48.1	0.91	0.63	25.1	27.7	0.61	0.81	33.5	27.7
rfq	0.47	0.75	40.6	25.9	0.33	0.53	25.2	28.0	0.63	0.64	34.2	28.7	0.69	0.69	34.2	26.4
smh	0.93	0.92	11.3	10.1	0.91	0.92	9.5	9.5	0.87	0.89	10.0	9.5	0.89	0.91	10.8	10.2
smph	0.98	0.97	4.9	5.7	0.97	0.97	5.3	5.6	0.96	0.96	5.1	5.5	0.97	0.98	5.5	4.8
smq	0.99	0.99	3.9	3.5	0.99	0.99	3.7	3.3	0.97	0.98	4.8	4.2	0.99	0.99	3.4	3.5
smpq	0.95	0.93	7.7	8.8	0.95	0.93	7.5	8.7	0.92	0.91	7.6	9.1	0.94	0.94	8.4	8.0

This table shows intraclass correlation coefficient (ICC) and standard error of measurement in percentage for indices of neuro-musculoskeletal performances included emdh, emdq, pfh, pfq, rfh, rfq, smh, smph, smq, smpq, lax on pre-op, 6th, 12th and 24th week following ACL.

This table shows coefficient of variation (V%) for indices of neuro-musculoskeletal performances included emdh, emdq, pfh, pfq, rfh, rfq, smh, smph, smq, smpq, lax on pre-op, 6^{th}, 12^{th} and 24^{th} week following ACL.

VII. Appendix: KOOS

Knee injury and Osteoarthritis Outcome Score (KOOS), English version LK1.0 1

KOOS KNEE SURVEY

Today's date: _____/______/______ Date of birth: _____/______/______

Name: ____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A4. Standing

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A5. Bending to floor/pick up an object

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A6. Walking on flat surface

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A7. Getting in/out of car

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A8. Going shopping

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A9. Putting on socks/stockings

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A10. Rising from bed

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A11. Taking off socks/stockings

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A12. Lying in bed (turning over, maintaining knee position)

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A13. Getting in/out of bath

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A14. Sitting

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A15. Getting on/off toilet

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

VIII. Appendix: IKDC

2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

Your Full Name____

Today's Date: _____/______/_____ (Day / Month / Year) Date of Injury: _____/______/_____ (Day / Month / Year)

SYMPTOMS*:

*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?

   ❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   ❑Strenuous activities like heavy physical work, skiing or tennis
   ❑Moderate activities like moderate physical work, running or jogging
   ❑Light activities like walking, housework or yard work
   ❑Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

	0	1	2	3	4	5	6	7	8	9	10	
Never	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Constant

3. If you have pain, how severe is it?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Worst pain imaginable

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?

   ❑Not at all
   ❑Mildly
   ❑Moderately
   ❑Very
   ❑Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?

   ❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   ❑Strenuous activities like heavy physical work, skiing or tennis
   ❑Moderate activities like moderate physical work, running or jogging
   ❑Light activities like walking, housework, or yard work
   ❑Unable to perform any of the above activities due to knee swelling

6. During the past 4 weeks, or since your injury, did your knee lock or catch?

   ❑Yes ❑No

7. What is the highest level of activity you can perform without significant giving way in your knee?
   ❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   ❑Strenuous activities like heavy physical work, skiing or tennis
   ❑Moderate activities like moderate physical work, running or jogging
   ❑Light activities like walking, housework or yard work
   ❑Unable to perform any of the above activities due to giving way of the knee

SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?

❑Very strenuous activities like jumping or pivoting as in basketball or soccer
❑Strenuous activities like heavy physical work, skiing or tennis
❑Moderate activities like moderate physical work, running or jogging
❑Light activities like walking, housework or yard work
❑Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a.	Go up stairs	❑	❑	❑	❑	❑
b.	Go down stairs	❑	❑	❑	❑	❑
c.	Kneel on the front of your knee	❑	❑	❑	❑	❑
d.	Squat	❑	❑	❑	❑	❑
e.	Sit with your knee bent	❑	❑	❑	❑	❑
f.	Rise from a chair	❑	❑	❑	❑	❑
g.	Run straight ahead	❑	❑	❑	❑	❑
h.	Jump and land on your involved leg	❑	❑	❑	❑	❑
i.	Stop and start quickly	❑	❑	❑	❑	❑

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

Cannot perform daily activities	0	1	2	3	4	5	6	7	8	9	10	No limitation in daily activities
	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	

CURRENT FUNCTION OF YOUR KNEE:

Cannot perform daily activities	0	1	2	3	4	5	6	7	8	9	10	No limitation in daily activities
	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	

IX. Appendix: K-SES

Appendix 2 – The K-SES instrument

A. Daily activities

Mark the box with the number that best represents how certain you are about the activity right now despite pain/discomfort.

How certain are you about:	0 = not at all certain									10 = very certain	
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1) taking a walk in the forest	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2) climbing up and down stairs	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3) going out dancing	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4) jumping ashore	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5) running after small children	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6) running for the tram/bus	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7) working in the garden	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

B. Sports and leisure activities

Mark the box with the number that best represents how certain you are about the activity right now despite pain/discomfort.

How certain are you about:	0 = not at all certain									10 = very certain	
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1) bicycling long distances	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2) cross-country skiing	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3) horseback riding	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4) swimming	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5) hiking in the mountains	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Not culturally adapted to English

Self-efficacy of knee function in patients with an ACL injury
Version 4, Copyright Pia Thomeé 2003

C. Physical activities

Mark the box with the number that best represents how certain you are about the activity right now despite pain/discomfort.

How certain are you about:	0 = not at all certain 0	1	2	3	4	5	6	7	8	9	10 = very certain 10
1) squatting	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2) jumping sideways from one leg to the other	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3) working out hard a short time after an injury	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4) performing a one-leg hop on the injured leg	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5) moving around in a small boat	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6) doing fast twisting	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Not culturally adapted to English

D. Your knee function in the future

Mark the box with the number that best represents how certain you are about the activity in the future.

	0 = not at all certain 0	1	2	3	4	5	6	7	8	9	10 = very certain 10
1) How certain are you that you can participate on the same activity level as before the injury?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2) How certain are you that you will not have new knee injuries?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3) How certain are you that your knee will not "break down"?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4) How certain are you that your knee will not get worse than before surgery (only for people who have had surgery)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Self-efficacy of knee function in patients with an ACL injury
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X. Appendix: Lysholm Scale

LYSHOLM KNEE SCORING SCALE

Instructions: Below are common complaints which people frequently have with their knee problems. Please check the statement which best describes your condition.

I. LIMP:

____ I have no limp when I walk. (5)
____ I have a slight or periodical limp when I walk. (3)
____ I have a severe and constant limp when I walk. (0)

II. USING CANE OR CRUTCHES

____ I do not use a cane or crutches. (5)
____ I use a cane or crutches with some weight-bearing. (2)
____ Putting weight on my hurt leg is impossible. (0)

III. LOCKING SENSATION IN THE KNEE

____ I have no locking and no catching sensations in my knee. (15)
____ I have catching sensation but no locking sensation in my knee. (10)
____ My knee locks occasionally. (6)
____ My knee locks frequently. (2)
____ My knee feels locked at this moment. (0)

IV. GIVING WAY SENSATION FROM THE KNEE

____ My knee never gives way. (25)
____ My knee rarely gives way, only during athletics or other vigorous activities. (20)
____ My knee frequently gives way during athletics or other vigorous activities, in turn I am unable to participate in these activities. (15)
____ My knee occasionally gives way during daily activities. (10)
____ My knee often gives way during daily activities. (5)
____ My knee gives way every step I take. (0)

V. PAIN:

____ I have no pain in my knee. (25)
____ I have intermittent or slight pain in my knee during vigorous activities. (20)
____ I have marked pain in my knee during vigorous activities. (15)
____ I have marked pain in my knee during or after walking more than 1 mile. (10)
____ I have marked pain in my knee during or after walking less than 1 mile. (5)
____ I have constant pain in my knee. (0)

VI. SWELLING

____ I have no swelling in my knee. (10)
____ I have swelling in my knee only after vigorous activities. (6)
____ I have swelling in my knee after ordinary activities. (2)
____ I have swelling constantly in my knee. (0)

VII. CLIMBING STAIRS:

____ I have no problems climbing stairs. (10)
____ I have slight problems climbing stairs. (6)
____ I can climb stairs only one at a time. (2)
____ Climbing stairs is impossible for me. (0)

VIII. SQUATTING

____ I have no problems squatting. (5)
____ I have slight problems squatting. (4)
____ I can not squat beyond a 90 degree bend in my knee. (2)
____ Squatting is impossible because of my knee. (0)

TOTAL____/100

INSTRUCTIONS: Please place an X on the line to indicate the amount of pain you have had in your knee(s) the past 24 hours. The scale ranges from "no pain at all" to the "worst possible pain".

RIGHT KNEE ____
no pain worst possible pain

LEFT KNEE ____
no pain worst possible pain

XI. Appendix: Conversion into Kcalories/day

Work done can be calculated by

$W = FD$

For calculation F, we need to calculate weight (weight and F are same things) weight= mg

(mass will be the total resistance in kilogram lifted during exercise) while g is acceleration due to gravity which is constant ($9.8 m/s^2$). If a person lifts 10 Kg in one session the weight of that 10 kg would be equal to

$w = mg$

$w = 10 * 9.8 = 98\ kg.m/s^2$

$kg.m/s^2$ is the unit of force so basically the F would be 98N.

For distance we need to calculate length of arc at specific angle

Length of arc for 90° angle (angle might change during each phase/session/exercise) = diameter× pi ×angle/360

Diameter would be calculated from the height of the patients (height/shin ratio)

After calculating the length of arc and force we can compute the amount of work done which can be converted into Kilo-calories as

1 Joule= 0.000238 Kilo-calories.

XII. Appendix: 7 Day Physical Activity Recall

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The Seven-Day Recall

PAR#: 1 2 3 4 5 6 7 Participant______________________________

Interviewer________________Today is____________________ Today's Date______

1. Were you employed in the last seven days? **0. No** (Skip to **Q#4**) **1. Yes**
2. How many days of the last seven did you work? ____ days
3. How many total hours did you work in the last seven days? ____ hours last week
4. What two days do you consider your weekend days? ______ ______ (mark days below with a squiggle)

WORKSHEET **DAYS**

	SLEEP	1 __	2 __	3 __	4 __	5 __	6 __	7 __
MORNING	Moderate							
	Hard							
	Very Hard							
AFTERNOON	Moderate							
	Hard							
	Very Hard							
EVENING	Moderate							
	Hard							
	Very Hard							
Total Min Per Day	Strength: Flexibility:	____	____	____	____	____	____	____

4a. Compared to your physical activity over the past three months, was last week's physical activity more, less or about the same?
1. More
2. Less
3. About the same

Worksheet Key:

An asterisk (*) denotes a work-related activity.
A squiggly line through a column (day) denotes a weekend day.

Rounding: 10-22 min.=.25; 23-37 min.=.50; 38-52 min.=.75; 53-1:07 hr/min. =1.0; 1:08-1:22 hr/min.=1.25